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CIGARETTE SMOKING AND HEALTH

An Extended Appraisal

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CONTENTS

FOREWORD

This essay - a critical review of recent scientific evidence - questions the fashionable imposition of an entirely unfavorable image of cigarette smoking. Undoubtedly, there will be a temptation to dismiss this effort as another evidence of contrived interests, but such a summary judgement should be resisted. The vast majority of the published work here reviewed was not funded by the tobacco industry and has emerged from the mainstream of biomedical research, quite unrelated to anything other than the serendipity of scientific inquiry.

This accumulation of favorable independent studies, and their increasing frequency over the last few years, reflects the second generation of sharper questions that naturally follow when initial interests mature around an issue. This report is not an apology of smoking: it simply accords equal and fair scientific value to the less publicized and desirable effects of smoking.

The reader will note that the mechanistic evidence supporting these effects is well developed and factually measurable in virtually all instances. Rationally this gives it a firmer ground, while the negative associations, as hypotheses, remain largely speculative. For a better understanding, the scientific, intuitive and logical

highlights of these new findings can be grouped around well defined themes.

First, there is the need to reevaluate the roles traditionally attributed to smoking in cancer, cardiovascular and respiratory diseases, in view of the numerous and new competing risk factors that continue to emerge.

Second, the evidence that smokers differ from non-smokers in a variety of physiologic, metabolic and psychologic traits of ecologic and genetic origin requires a reconsideration of epidemiologic studies which have assumed that smokers and non-smokers are alike in all respects other than smoking. This assumption especially invalid for studies of diseases with psychosomatic components, notably cardiovascular diseases.

Lastly, there is evidence of considerable protective effects of smoking for certain cancers, colon disorders, hypertension, obesity, and neurological conditions.

Health has undeniable subjective components, defined by individual perceptions of functionality, coping, relaxation, and all-around performance. Thus, a complete overall evaluation should include a fair assessment of existential benefits, since it is transparent that

from their habit smokers attain tangible rewards in behavior, performance and pleasure. In all justice, these gains cannot be deplored as morally reprehensible: not as we strive for individual happiness and free choice, and certainly not in the objective context of science.

Today it is difficult to discuss smoking in dispassionate scientific terms, largely because the dialogue has gone beyond science and into volatile political terrain, and has turned increasingly ambiguous since initial altruistic intents have given way to anti-smoking enterprises with power interests of their own. It is now time to re-examine the scientific record as a matter of legitimate inquiry and intellectual integrity. How tobacco is eventually viewed by society is a cultural and ethical question, which science can help solve only with an impartial and comprehensive assessment of reality.

OVERVIEW

Government and voluntary agencies justify massive campaigns against smoking by the widely publicized notion that smoking kills. These efforts have significant implications for social and labor structures and national economies, while ostensibly directed at preventing disease and increasing longevity.

Yet, it is recognized that smoking is pleasurable and not presently life threatening to individual smokers. Furthermore, it is impossible to predict who will be affected by smoking attributed diseases, whether smoker or not. Only a fraction of smokers - even heavy smokers may develop diseases that are also frequent among non-smokers. The notion that smoking kills is thus restricted to statistical differences in disease frequency, and it is intuitive to most people that over-simplified assumptions make this notion extreme and, more to the point, arguable.

Associations that suggest no more than putative risk have been promoted to the impressive status of causes. Parallel overstatements commonly apply to other issues besides smoking, and are widely perceived as an acceptable and even necessary expression of an educational mandate in public health. The merits of this pragmatic reasoning are beyond dispute, but it is clear that a policy of such vast

social impact could easily invite abuse, and calls for restraint. Limits would be imposed by responsible administrative and political action, but the temptation to overreach is seldom resisted in a climate where it is apparent that even public health can be perceived as an instrument of power, and only incidentally as a mandate of trust. In the end however, policy cannot ignore the shifting weight of emerging scientific evidence as old theories and assumptions evolve in the light of new findings.

Studies in epidemiology have been and are providing the substantive base of knowledge in smoking and health, and a review of their structural assumptions helps to understand how this knowledge emerged, and how it has changed.

Assumptions were not born by design, but were latent in the methodology and undeveloped frame of reference of early epidemiologic studies. By necessity, these sought precise identification of exposed and unexposed groups, and cigarette smoking offered an unmatched opportunity to achieve this all-important separation. In fact, it remains the single major environmental factor that allows dichotomizing exposure fairly accurately; most other exposures - to pesticides, pollutants, diet,

radiation, etc. - being fraught with unresolvable measurement uncertainties.

This singular advantage was coupled with and fostered the assumption that smokers and non-smokers were otherwise equivalent in all other respects, thus producing an experimental framework that made smoking studies easy and popular. This belief, however, is certainly mistaken because of the demonstrable self-selection of smokers and non-smokers. (This report p.).

The widespread use of simplistic assumptions generated an unwarranted sense of security, in that it virtually guaranteed reproducible results. As a consequence, the reassuring concordance of hundreds of studies has repressed many concerns that properly should have been raised. Still unanswered is the extent to which this apparent coherence is the artifact of common weak assumptions and study design, or the reflection of a causal reality.

This dilemma first surfaces in the partitioning of total lung cancer incidence among the various agents regarded as having fractional causative roles. At the height of reductionist thinking, it was asserted that about 10% of lung cancers occurred in non-smokers for unknown reasons, while all others were determined by smoking (US DHEW 1964,1979; US DHHS 1987). Since then, a number of

competitive risk factors have been identified, beginning with asbestos, other respirable solid state and gaseous carcinogens, and naturally-occurring or technologically-enhanced ionizing radiation. Asbestos alone was deemed responsible for some 50,000 lung cancer cases a year, in an official report backed by the highest U.S. government authorities (National Cancer Institute 1978). The same report stated that an additional 10-20% of lung cancers were caused by other occupational carcinogens unrelated to smoking. The report was the target of heated dispute between those who sought support for labor causes, and those reluctant to weaken their stance against smoking. More recently radon and its daughters have been officially linked to at least 20,000 lung cancer cases or some 20% of all annual mortality (US EPA 1987).

Epidemiologists make a theoretical argument that for diseases with multiple risk factors the sum of fractional causative responsibilities may well be in excess of 100%. Nevertheless, it is undeniable that the magnitude of this excess is directly related to the uncertainties of factor attributions. In the case of lung cancer, it is a forgivable suspicion that divergent interests influence causality claims.

Reductionist thinking also affects the majority of studies that have assumed a random distribution of individual traits among smokers and non-smokers. Plain observation tells that virtually all males and

a majority of females try smoking, yet only about one-third end up enjoying it more or less permanently -- an indication of differential predisposition or, at least, of some intrinsic difference. Numerous studies have mapped a mosaic of substantial differences in the personalities, behavior and metabolism of smokers. These differences are not caused by smoking; rather they allow a reasonably accurate prediction of who may or may not become a smoker. (This report p.).

Among these differences one can find genetic susceptibility to cancer and other diseases, and different physiologic affinities for a variety of potential carcinogens. Metabolic, behavioral, and personality traits are likely to be responsible for selective susceptibility to cardiovascular diseases (CVD), where the reasons for the excess morbidity and mortality attributed to smoking become rather weak on close scrutiny, compared to stronger determinants such as genetics, obesity, hypertension, blood lipids and cholesterol, stress, gender, socioeconomic status and others.

Prominent observers have often warned that the smoking-CVD correlation is equally explained by the hypothesis that CVD-prone individuals are also more likely to smoke (Stallones 1980,1983). Such propositions have been tested indirectly by several large intervention trials set up in the U.S. and abroad to investigate the impact of

reducing perceived CVD risk factors. These studies followed prospectively, often for over a decade, tens of thousands of subjects randomly assigned either to groups living habitual lifestyles, or to groups that were made to change their dietary, exercise, smoking and drinking habits, and that had undergone hypertension treatment. A common outcome has been that intervention groups experienced equal or slightly higher morbidity and mortality than the groups left alone (Werko 1987).

On an even larger epidemiologic scale, CVD mortality has been steadily declining in the U.S. and other developed countries over the last decades. In some countries, notably Italy and Japan, such declines occurred in the face of rapidly and significantly increased rates of per capita smoking, saturated fat and caloric intake and alcohol consumption (Nicolosi 1988, Ueshima 1987).

The CVD-smoking correlation may thus reflect the inclination to smoke of a population segment already CVD-prone, while the apparent correlation for lung cancer may have to be shared with other risk factors, and to be diminished by the probable susceptibility of at least a fraction of smokers. Indeed, tobacco smoke cannot be defined as a complete carcinogen by classical experimental methods in animals, but only as a weak promoter. Obviously, even an accessory responsibility would not exonerate smoking, but the

situation lends appeal to the opportunity for controlling more easily controllable factors, and for warning susceptibles. At the very least, it indicates that the sum of diseases traditionally attributed to smoking is entirely excessive, and may be narrowed still by future findings.

It will be argued that smoking should be opposed even if its contributions to disease were to be much less than thought today, on the grounds that smoking is not a necessity. This, however, raises nettlesome ethical and political issues, unless one advocates the odious need of paternalistic intervention for the protection of presumably incompetent masses. Besides, it is inconsistent to assert that smoking is not a desired practice, when perhaps nearly a third of humanity chooses to smoke despite warnings to the contrary. Such an assertion becomes even more difficult, in view of independent scientific data telling of significant behavioral and health benefits. (This report p.).

A voluminous literature leaves no doubt about the role of nicotine and smoking in stimulating alertness and cognitive capacity. For many, this develops into a pleasant dependence, not unlike the psychologic dependence on food and water. The amphoteric effects of nicotine and smoking in sedation and arousal are well documented, and represent a considerable coping aid for the majority of smokers

under daily stress. The benefits of those rewards are the main incentive for smokers, and the source of tangible existential advantages. The adverse image given to smoking has prevented more substantial scientific attempts at their measurement, and ironically they have been misused to compare smoking with dangerous addictions to drugs and alcohol. Intuitively this is not a tenable parallel: contemporary culture assigns the pejorative of addiction only to abuses that lead to loss of personal self-control and responsibility, and to forcible behavior injurious to self and others.

Indeed, without such qualifiers everything that is habitually taken becomes an addiction, including bread and the air we breathe. Smoking lacks the negative attributes of addiction. On the contrary, its reinforcement of performance and coping can only have positive outcomes for individual and social behavior.

Whatever precautions may be warranted in smoking, - and undoubtely there are some - they should be determined by the total balance of smoking contributions to health and disease, much as it happens for other desirable activities presenting residual risk, such as sports, a plentiful diet, and so on. A growing number of studies indicate that this balance needs to be revised in a positive direction.

It has been known for a long time that the frequency of Parkinson's disease in smokers is less than half that in non-smokers, and more recently, there has been speculation that smoking might be of help in mental disorders and Alzheimer's disease. (This report p.).

For colon cancer, evidence indicates that the incidence in smokers may be about 30% less than in non-smokers. (This report p.). This suggests the potential of thousands of additional colon cancers if smokers did not smoke, unless of course smokers died of competing diseases first, or were resistant to colon cancer independent of smoking. Studies have noted the specific action of smoking and nicotine on the motility and mucus secretion of the colon, and have speculated on the reasons for the observed protection, which extends to other colon ailments. Ulcerative colitis is at least 50% less frequent in smokers, while Crohn's granulomatous enteritis is two or three times more frequent. Ulcerative colitis is the more common ailment and - although seldom a direct cause of death - it accounts for untold lifelong suffering and loss of productivity for millions of patients around the world.

A vast literature documents that smoking depresses endogenous estrogen secretion and thus reduces the risk of estrogen-dependent breast and endometrial cancers by as much as 50% (This report p.). There is also indication that smoking increases endogenous estrogen

production in males, suggesting the possibility of beneficial effect for androgen-related cancers and diseases.

Other studies give evidence that mean blood pressure is lower in smokers, hypertension being a major recognized risk factor for cardiovascular disease. (This report p.). As mentioned, several large intervention trials failed to show that quitting or reducing smoking results in lesser CVD mortality, thus challenging the alleged causal linkage. That smoking helps control weight is perhaps of greater significance in CVD incidence. Smokers are consistently lighter, and those who quit gain as much as 20% in weight (This report p.). The adverse effects of such gain have been recognized for decades in actuarial tables of life insurance underwriters, and could result in over 100,000 excess deaths per year in the U.S. alone.

A further major consideration is the substantial body of data that links CVD susceptibility to behavioral and personality traits of probable genetic origin. (This report p.). On these grounds it is likely that susceptibles may experience subclinical cardiovascular deficits early in life, and turn to smoking for compensation. This hypothesis seems to fit the evidence more reasonably than the hypothesis of causation.

As noted above, the positive effects of smoking are grounded in much firmer epidemiologic evidence than the negative associations. Estrogen depression is a factual and exceptionally well measurable effect, with physiologic, preventive and therapeutic functions long recognized and undisputed in mainstream medical knowledge. The results of smoking are also directly measurable in appetite and weight control and in the moderation of hypertension, two often paired risk factors of factual and non-hypothetical significance in the pathogenesis of circulatory and other diseases. (This report p.).

The roles of nicotine are extensively documented in regard to its stimulant and sedative effects, and better and better light is being shed on its function in colon motility, the prevention of Parkinson's disease, and more recently in the treatment of Alzheimer's disease. (This report p.).

Observations continuously being reported in the epidemiologic literature make it obvious that an increasing number of potential risk factors - other than smoking - are associated with lung cancer incidence. (This report p.).

answers

On the other side, the ~~negatives~~ of smoking and disease remain statistical associations with no support of factual mechanistic data. Cancers

~~Negative~~ inferences have been formulated around convenient

hypotheses that remain provisional, and that have yet to be tested and validated scientifically. In fact, these hypotheses have failed the most decisive test applied to date, namely the numerous and massive population and clinical intervention trials conducted around the world to measure the effects of reducing smoking and other risk factors. The clinical and public health communities are still reeling under the impact of these outcomes and are frantically trying to make sense of their broken expectations, while the public has been kept generally uniformed of these failures.

No study of tobacco usage would be complete without an objective measure of the behavioral, existential and emotional benefits derived. This will first require the recognition that smoking is important for at least a third of humanity, and the adoption of standardized methods for obtaining comparable data in different settings.

The divergent characteristics of smokers and non-smokers offer a fertile field of research. This divergence could explain different responses to environmental and behavioral stimuli, different propensities to seek smoking as a desirable coping aid, and intrinsic susceptibilities or resistances, especially to cardiovascular diseases. In particular, the protection offered by smoking against certain colon disorders, hormone-dependent cancers, and certain neurological

diseases should be studied to determine the underlying mechanisms and to find ways to reinforce them.

Regrettably, today the study of smoking and health requires an extraordinary effort of impartiality, given the accumulation of the emotional and cultural animosities forcibly imposed during the last decade. That many scientists also partake of this bias is a further difficulty. For instance, few stop to consider that nicotine is a mild cardiotonic and a benign versatile CNS stimulant or sedative, which patients may take because of a cardiovascular or psychosomatic deficit that in itself is a harbinger of disease.

Overall, the current picture of the health benefits of smoking is substantial, both as arguments that reduce traditionally assigned responsibilities, and as outright measurable contributions to health. This ought to be sufficient ground for pause, especially if we add the growing appreciation that even the most bland of human activities are not devoid of risk. That this evidence could emerge in a climate generally hostile to smoking is in itself remarkable, and tells that more is to be found. Indeed, while the evidence on hand may not be sufficient to render a definitive judgement about smoking, it suggests an overall beneficial influence that only a more open minded approach could deny or confirm.

METHODOLOGICAL ISSUES

Much of the perception of smoking's role in health derives from the epidemiologic literature. The complex nature of this body of information demands insight into the general process of epidemiologic inference and the sources of bias that can affect the results and interpretation of epidemiologic studies.

Epidemiology produces action-demanding results often imposed on the public with vast social consequences, and is thus laden with political and ethical implications. As social engineers with unassailable better health agendas, epidemiologists hold considerable clout, and because balance and skepticism are not the usual disposition of man, there is a concern that inferences of causality in epidemiology ought to be factually supported. Aware of this concern, epidemiologists have mounted extraordinary efforts to explain how they arrive at causative conclusions. Not surprisingly, the laboriousness of these efforts is directly related to the logical fragility of their statements (MacMahon 1970, Susser 1973, 1986, Rothman 1986).

Currently, the weaving of results from various epidemiologic studies into an hypothesis of causality requires more than consideration of statistical significance or an accumulation of replicated findings.

Several schemes for judging a potentially causal association have been suggested. The 1964 Surgeon General's Report on Smoking and Health (DHEW 1964) suggested five criteria for judging an association: Strength, consistency, specificity, temporal sequence, and coherence. In addition to these, Hill (1965) suggested biological gradient, plausibility, experimental evidence, and analogy. Recently, Susser (1986) expanded this list, providing an indication of the relative importance of each criterion in assessing hypotheses of causality.

"Strength" is probably the criterion intuitively used most often for judging causality. It refers to the magnitude of a risk estimate (or "effect size") such as relative risk, ratio of incidence rates, odds ratio, etc. An association between some exposure and a disease outcome with a large risk estimate is less likely to result from confounding or other biases than one with a small risk estimate. Susser considers a very high relative risk or other measure of effect to be a strong affirmative criterion. However, as Rothman (1986) points out "...the strength of an association is not a biologically consistent feature but rather a characteristic that depends on the relative prevalence of other causes." In some schemes, "dose-response" is included under "strength." Hill lists this criterion (which he calls biological gradient) separately, but in any case, it reflects the likelihood that a potentially causal association would demonstrate a quantifiable

relationship between the outcome and various levels of exposure. While non-causal associations might intuitively seem less likely to demonstrate a dose-response relationship, this result is possible if a confounding variable has a similar relationship to an exposure of primary interest.

For example, bronchitis is consistently and strongly associated with the amount of air pollution. However, air pollution is found to vary systematically and directly with the density of urban settlement. It is also known that population density varies inversely with socioeconomic level or residential areas, and that the more crowded a population is, the more likely it is that respiratory infections will spread easily. Thus, while air pollution might seem to cause bronchitis, the truth could be that the overcrowding and high population density found in areas of low socioeconomic status confound this apparent relationship. Density and social factors which could cause bronchitis by facilitating the spread of infection, could also cause air pollution by a concentration of the use of domestic and industrial fuels and motor transport. In this case, crowding is a confounding variable in the air pollution/bronchitis association. Thus the size of an observed effect may be misleading in assessing causality, and cannot be the the sole determinant of causality claims.

"Consistency" refers both to demonstrated repeatability under different conditions and to similar results across different subgroups of the same study. The key to the first part of this criterion is that results must be repeatable under different study circumstances; it is not met by repetitions of essentially the same study. According to Susser, high positive consistency is strongly supportive and high negative consistency strongly detractive. However, it is clear that the adoption of flawed assumptions - e.g. that smokers and non-smokers are otherwise psychosomatically identical - would lead to results that are consistent, but also consistently biased.

Indeed, the "specificity" of an association, i.e. a cause resulting in a single effect or an effect resulting from a single cause, has some merit for evaluating a potentially causal association, but its absence should not nullify a causal relationship, and its presence lends little support for one. There are many instances where one cause can have several effects. Even high specificity, according to Susser, adds plausibility to a causal, claim but its absence does not detract from the claim. "Specificity in the causes of a given effect is persuasive; specificity in the effects of a given cause is much less so."

Clearly, "temporal sequence" requires that the exposure or cause precede the outcome or disease if the former is causing the latter.

Failure of an association to meet this criterion is the ultimate evidence that it is not causal.

"Coherence" usually refers to biological plausibility. That is, does the hypothesized association fit with accepted principles? To fulfill this criterion, an association could not conflict with existing information, but in the absence of such information should be plausible, given the current state of knowledge. In Susser's scheme, biologic coherence is not a particularly strong criterion. He adds theoretical, factual and statistical coherence as criteria. The latter refers to a dose-response relationship, which is supportive of causality.

Susser (1986), probably concerned about the rational weakness of these criteria, suggested adding a firmer decision test, namely predictive performance. Indeed any causal hypothesis would be convincingly corroborated if the removal of the presumed cause - or causes - consistently abated the disease. Although philosophers will argue that even this gives no definitive proof of causality, it would be quite sufficient evidence for pragmatic public health considerations. Yet, with minor exceptions, this criterion has not been met convincingly for chronic multifactorial diseases, as noted before (Werko 1987, Nicolosi 1988, Ueshima 1987).

From this cursory review, it is clear that the understanding of bias is essential to epidemiologic thinking and critical evaluation. Bias, or distortion, exerts its effect throughout the epidemiologic process. By far the most serious type is systematic bias, but random bias, at the very least, tends to weaken estimates of effect. Feinleib's "stages" of an epidemiologic study provide a good framework for a consideration of bias (Feinleib 1987). The first stage of an epidemiologic study deals with the definition of the disease and the exposure or risk factor. The use of unstandardized procedures for assigning cause-of-death or for diagnosing a disease is too often overlooked in the conduct of a study. Yet, differential diagnosis associated with exposure, or misclassification of the measured outcome easily can account for apparently positive or negative findings.

In particular, death certificates are notoriously inaccurate, reflecting medical care utilization, certifier training, familial concerns, and other factors unrelated to the actual causes of death. Information available on exposures varies widely with study setting, and an association or its interpretation may be highly dependent on the quality of information available, or on the definition of exposure in a particular study.

For example, we may be more likely to assign radiation exposure of some workers as a cause of cancer simply because we can measure it more easily and accurately than their chemical exposures (for which we usually must employ a surrogate measure such as job title). Similarly, tobacco exposure is easily estimated in a variety of ways such as type of tobacco product, intensity of use, duration of use, estimates of dosage, etc. (Feinleib 1987), but these estimates are imprecise, easily biased, and the different metrics employed may result in different conclusions. Furthermore, questionnaire-derived estimates of tobacco exposure are obtained frequently from next-of-kin, who have been shown to under-report the amount which a study subject smoked, (Herrmann 1985), and even when accurate, may not be a valid measure of exposure at the biochemical level, as reflected by expired air carbon monoxide and serum thiocyanate (Vogt 1979, Pettitti 1981). Nor do the cigarette yields determined by the Federal Trade Commission, which are then used to estimate exposure to smoke components, accurately reflect relative intake of nicotine, carbon monoxide, or tar (Gori 1985, Zacney 1988). To complicate matters further, cigarette pack sizes have been changing, and reports by smokers or surrogates of consumption by packs-per-day have different meanings in different countries and time periods (Kozlowski 1986).

The stage of a study where a sample is selected is the most vulnerable to bias. Cohort studies, in which study subjects are chosen based on their exposure status, are less likely than case-control studies (in which subjects are selected based on disease status) to suffer from selection bias. However, bias can result from differential diagnosis, follow-up completeness, distribution of covariables in the different exposure categories, or the differential presence of incipient disease. In case-control studies, one must assure that the probability of selection into the study as a case or as a control is independent of the probability of exposure. As in cohort studies, selection bias in case-control studies can result from biased sampling procedures, self-selection of volunteers, non-response, inaccurate assignment of disease status, or differential availability of records. These difficulties would tend to produce a bias towards the null, i.e. no assumption.

Frequently, bias enters through a questionnaire design that influences responses, prior knowledge of exposure or disease that influences the conduct of an interview, and misinformation (substitution bias) resulting from surrogate respondents, etc. Certainly, there are other sources of bias which may not be apparent initially, and it is prudent to consider all possible sources in assessing the hypothetical causal nature of an association and in

determining how much of the multifactorial etiology of a disease it explains.

Data processing and analysis are less often sources of bias, although failure to consider whether a data set fulfills the assumptions necessary for using a particular statistical method is seen frequently. One example of this source of bias is in the mistaken "rare disease assumption" which underlies the equivalence of an odds ratio estimate from a case-control study with the risk ratio (relative risk) estimate derived from a cohort study. Feinstein (1986) has pointed out that even when we document that the rate of disease in an unexposed population is indeed very low (i.e. that it is a rare disease), modern diagnostic methods may later reveal a very high incidence of the disease among the unexposed. This would result in erroneous estimates of the relative risk in case-control studies based on prevalent cases.

Another subtle, generally unrecognized bias operates on the entirety of scientific literature, and bears great potential for distorting the knowledge base which links smoking and disease. Greenland (1987) discusses this "publication bias" in detail, noting that any compilation of results from published studies may be biased if the studies included in that compilation or meta-analysis are a biased subsample of studies in general. Moreover, most scientists generally

believe that journals preferentially accept papers reporting an association over papers that do not. Given the omnipresent, though mistaken perception that smoking is a risk factor for a multitude of diseases, one can easily see the potential difficulty in publishing a paper with negative results which do not conform with this perception. This "publication bias" may also extend to selective submission of original work (Salone 1988). The real misfortune associated with these types of baises is that these negative results cannot even be evaluated for their validity, nor can the bias be proven.

The described uncertainties, and others, have created still insurmounted difficulties in the epidemiologic definition of causation for multifactorial chronic diseases. In order to appreciate the situation better, it is useful to review the basic notions of causality. This concept is acquired at an early age as a means to understand and cope with the physical world. By observing we deduce cause and effect, and the predictability of observations leads to forecasting future outcomes and guides our decisions.

The ancients discovered the mind, and cultivated abstract causal concepts that could be structured in a rational system of logic and mathematics, leading to precise deductions and inductions. Their predilection for the abstract dominated through the middle ages, until Galileo and Newton applied rational thinking to physical

events, giving birth to the scientific method and modern science. Despite the protestations of pure scientists, science continues to bear a successful utilitarian imprint and strives to define inducible results, to forecast and thus to be normative.

The stochastic nature of the physical world makes it appear less perfect, when compared with the exact formality of logic and mathematics. Notions of causality in the real world would have to accommodate for uncertainty, and have been transformed into the concept of hypotheses to be proved or disproved. Philosophers have long argued on the merits of these concepts, from Bacon to Newton, from Pascal to Hume, from Leibniz to Einstein and Popper. Their writings illustrate an historic reluctance to concede that the precision of logical conclusions can seldom agree with the inevitable approximation of physical observations. Today it is widely accepted that for issues of causality in the real world, only hypotheses can be formulated, which can be tested with varying degrees of precision and assurance. The attending uncertainty varies from the close precision of fundamental physical laws, to the vagaries of complex non-linear systems, such as the weather and financial markets.

Unfortunately, epidemiology is closer to the latter than to the former, as attested by the consuming preoccupation of epidemiologists in justifying their definition of causality. On close analysis, their

canons turn out to be guidelines for judgement tailored to a mandate for prudent public health policy, but are too vague and ambiguous as scientific propositions, or even for the definition of causality as perceived in everyday life.

Although the probability of hypotheses being true varies in a continuous range from virtually true to quite uncertain, most real life decisions are discontinuous because they demand unambiguous statements exemplified by yes or not choices. These choices, determined by the information available at the moment, cannot always be correct. Yet we decide, largely on the basis of logic perceptions that identify sufficient and necessary causes.

In common parlance, causes that are invariably and demonstrably sufficient for a given outcome, such as the earth's rotation causing day and night, are accorded the highest reliability. Causes that are not always sufficient but must be invariably present and necessary for a given outcome are considered equally decisive in making unambiguous choices. Necessary and sufficient causes are usually identified by end result observation and do not require mechanistic understanding. On the other hand, an outcome could also have several independent and unrelated causes that individually do not appear sufficient or necessary. In such instances, and in order to

identify reliably any one of these facultative causes, it is necessary to have satisfactory mechanistic evidence at hand.

As a further clarification we also speak of proximate causes, defined pragmatically as those elements of a situation that change or are amenable to intervention. We do not think of the lung as the cause of lung cancer, although it is an essential element of the event. Also, it is the throwing of a switch that turns the light on, not the associated wiring, etc. Proximate causes are not always single entities, but several synchronous or sequential factors may be involved. In such instances, a satisfactory sequential mechanistic understanding of the multifactorial relationship must be available for a reliable definition of composite causality.

Necessary, sufficient and facultative causes - and composite clusters of such causes - allow definitive decisions that for all practical reasons ignore residual uncertainties. Beyond these accepted concepts of causation we identify events that may be associated with, but are neither sufficient nor always necessary for an outcome. An example is the association of cigarette smoking and lung cancer. These associations do not allow unambiguous decisions but can be used to formulated provisional hypotheses, which only if confirmed by mechanistic understanding may lead to the definition of

facultative causes. In all other cases, the associations are open to all interpretations.

Under these premises it is surprising that we have come to speak of causes for the most prevalent chronic diseases of today, since not a single factor associated with these diseases meets the commonly accepted definition of causality. None of the so-called causes (with the exception, perhaps, of rare genetic defects), can be defined convincingly as either the sufficient, necessary or facultative motive of cancer, cardiovascular or chronic respiratory diseases.

Epidemiologists, however, have been under forceful pressures to translate the same clear-cut message of causation that was possible for the well identified causes of infectious diseases to the much weaker circumstances associated with multifactorial chronic diseases. Rothman (1986 p.17) clearly sums up the situation when he states:

"Despite philosophic injunctions concerning inductive inference, criteria have commonly been used to make such inferences. The justification offered has been that the exigencies of public health problems demand action and that despite imperfect knowledge causal inferences must be made."

In fact, for most multifactorial chronic diseases a definition that meets elementary standards of evidence does not allow to speak of causality, but at best of putative risk factors. In the definition of causality for such diseases the central difficulty stems from the unpredictable interactions of a multiplicity of associated factors, each with a significance and biological mechanism that are unknown or speculative. A century ago, Koch could confidently advance postulates of causality fully met by infectious agents: they may not always be sufficient, but they are certainly necessary and proximate causative factors. Not so for the chronic diseases prevalent today.

The circumstances of "sufficient" cause, i.e. the minimal set of conditions which produce a disease, are not verified for the association between cigarette smoking and disease. Rothman (1986) presents an enlightening discussion and points out that smoking (even explicitly defined as he requires) will not cause cancer in everyone, and thus it is not a "sufficient" cause. Furthermore, when other components of the causal connections that act to produce cancer are unknown, there is a tendency to assign an equal risk to all individuals whose status for the recognized components of the connection is known. We do this because of our ignorance of the distribution of those other unknown factors. Yet, failing to remain cognizant of this underlying reason, we forget that our convenient assumption of equality is not real.

The inherent lack of experimental control in epidemiologic studies, allows spurious relationships to surface in a variety of ways. Unrecognized and uncontrolled confounding, or unaccounted-for correlations between the disease outcome of interest and other factors are not always obvious to the trained reader, and are seldom appreciated by the untrained layman. Concepts such as statistical significance frequently lose their meaning in the media distillations of scientific literature, commonly the sole source of scientific information for the general public. To most people, "excess mortality due to smoking" is exactly that - excess. They are not concerned that the "excess" may be small, not statistically significant or hopelessly biased by uncontrollable confounders. One could hardly expect that the public would be skeptical enough to consider possible alternative conclusions.

On the other hand, as mentioned before, the evidence for the desirable effects of smoking is based on hypotheses that already have obvious and measurable mechanistic support. Antiestrogenic effects, blood pressure and weight reduction effects are fully demonstrable, and correspond not to hypothetical causal inferences, but to therapeutic prescriptions long established in medical practice. The protective effects in Parkinson's - and likely in Alzheimer's disease are being mechanistically elucidated. The mild cardiotonic

and benign behavioral effects are established and measurable facts, not mere free-standing hypotheses.

The positive consequences of smoking are indeed grounded on much firmer evidence, as compared with the still speculative character of the contrary associations.

That epidemiology has served human kind generally well so far is the result of the simplified context of the now conquered infectious diseases, triggered by precisely identifiable casual agents. Future contributions of epidemiology to human health are likely to be much less measurable, given the confusing mix of multifactorial combinations in the pathogenesis of modern chronic diseases.

Ideally, the discovery of facts and causal connections in the real world should be an impartial process, unbiased by preconceived policy agendas. Science should offer factual information as a basis for policy making, but policy making pressures are seldom conducive to good science (Lanes 1985). This is especially true for modern epidemiology, where a data base with a high margin of uncertainty is subject to pliable interpretations under different ethical motivations, value judgements, cautions, fears, economic and professional

interests, cultural preferences and even different ideas of charity and benevolence. This ambiguity allows creative uses of epidemiology in support of different interests, from government agencies to rich charities, from well-meaning philanthropists to all sorts of advocates.

Under heavy inducements, epidemiologists have searched in vain for an independent validation of their efforts. In the end the criteria for inference of epidemiologic causality have been elaborated by epidemiologists, for use by epidemiologists, usually with the peculiar statement that acceptance of such canons generates consensus, and that consensus certifies causality. Thus, part of the problem in smoking and health is that most epidemiologists have been entranced by their consensus, and have failed to look hard enough for alternative hypotheses and variables that would put consensus in question. It is a tribute to a few inquisitive scientists that evidence for such alternative hypotheses has accumulated, the hostile climate notwithstanding.

CORONARY HEART DISEASE

The etiology of coronary heart disease (CHD) is a complex network of inter-related factors, some of which seem obvious (e.g. hypertension) and some which might not be expected e.g. occupation (Buring 1987), estrogen use (Wilson 1988) , (Abbott 1988), and low altitude (Weinberg 1988)). In the United States, over 550,000 deaths each year are due to coronary heart disease, but in the last twenty years or so, the mortality rates for this disease have declined steeply. The decline is real, and occurred uniformly among blacks, whites, males, and females (Friedewald 1986). This decreasing CHD mortality has been attributed to changes in lifestyle among Americans, as well as to improved medical care (Goldman 1984, Gillum 1984). Among the lifestyle factors usually cited as contributing to the decline in CHD is the reported reduction in the proportion of people who smoke cigarettes. However, this reduction may not be as large as we might think. Nationwide, production of cigarettes increased up to 1981, and is now stable. Commercial disappearance of cigarettes, based on tax receipts, has decreased only slightly.

Between 1976 and 1980 the percentage of male and female smokers fell 3.6% and 2.6% respectively (NCHS 1982); since 1964, the percentages declined 27% in white males and 13% in white females, with blacks in between (US DHEW 1980). The proportions of heavy smokers, however, rose in women, declined in black males, and remained unchanged in white males. Thus, the uniformity of reduced CHD mortality among race/sex groups is incongruent with the rates of cigarette usage among these groups. In particular, the decline in CHD mortality among women and blacks is not explained by what is known about their change in other risk factors, as well (Blackburn 1986). Other descriptive epidemiologic evidence is equally incongruous: There is little increased risk of heart attack among smokers living in countries with low intakes of cholesterol and saturated fats; and smoking is not a CHD risk factor for Japanese men living in Japan, although it appears to be one for Japanese men living in Hawaii (Kieller 1986). The coronary heart disease mortality risk among Finnish women far exceeds that among for women in Denmark and Norway, despite the comparatively higher prevalence of smoking among the latter (ERICA 1988). Rural Puerto Rican

males had lower CHD mortality than urban males, although the percentage of current smokers was higher in the rural areas (Garcia-Palmiere 1988). Indian men living in London had strikingly higher mortality from coronary heart disease than men of European or West Indian origin, but had half the percentage reporting that they smoked, compared to the other two groups (Miller 1988). These anomalies reflect both the multifactorial etiology of the disease, and the conflicting evidence as to the magnitude of the CHD risk attributable to cigarette smoking.

Much of the evidence implicating cigarette smoking as a risk factor for cardiovascular mortality comes from the Framingham Heart Study, a long-term prospective investigation which began in 1948. This study has followed a cohort of 5,209 men and women with biennial examinations including physical examinations, complete histories, ECGs, and multiple blood chemistry measurements (Kannel, et al 1987). Data from Framingham, though not totally consistent (e.g. never-smokers had a higher rate of cardiovascular events than ex-smokers and only slightly lower than current smokers), and of dubious representativeness (e.g. only four black

subjects were included in the original cohort), indicate that the habit of smoking cigarettes appears to be an independent contributor to the occurrence of coronary heart disease and that the effect is related to dose (i.e. number of cigarettes smoked per day), but not to duration. (Kannel 1987, Gordon 1975)

Lack of excess risk among ex-smokers was attributed by the Framingham investigators to the notion that "smoking has a non-cumulative, transient, reversible triggering effect rather than a direct influence on atherogenesis." (Gordon 1985) Yet, the British Regional Heart Study (Cook 1986), a prospective non-intervention study of 7,735 middle-aged men, found little difference in heart attack rates among current smokers and ex-smokers (including men who quit smoking more than twenty years prior). Willett, et al (1987), in a study purporting to find a 2.5 -fold increased CHD risk among women who smoked only 1-4 cigarettes per day, nonetheless found insignificant differences in CHD risk for ex-smokers vs never-smokers.

A similar study among Japanese men in Hawaii also failed to find a consistent relationship between smoking and coronary heart disease. (Reed 1987) In this investigation, 8,006 men aged 45-68 were given baseline examinations during 1965-1968, and then received follow-up exams two and six years later. A rigorous protocol ensured that ascertainment of deaths occurring in this cohort was complete and that the hearts and associated structures could be acquired for detailed pathologic evaluation. Between 1966 and 1982, 1,381 of the original 8,006 men died. 290 of the men had a protocol autopsy, and of these, 230 had gradable coronary arteries. The degree of atherosclerosis was determined using the American Heart Association panel method. The atherosclerosis score for each subject was used as the dependent variable in a multiple regression analysis to determine the significant risk factors. Age-adjusted mean atherosclerosis scores showed no trend by cigarette pack-years. These scores were 3.0 for zero pack-years; 2.5 for 0-14 p-y, 3.5 for 15-38, and 3.2 for 39-164.

Still another long-term prospective follow-up study of men found smoking not to be a significant risk factor for coronary heart disease

(Menotti 1982, Farchi 1987). In this study, 1,712 men aged 40-59 from two rural Italian villages, representing almost the entire population in that age group, were followed for twenty years after an initial physical examination and questionnaire survey. Cause of death information was obtained from multiple sources, coded by the research team, and the cause used in the data analyses was independent of that on the official death certificate. This approach, if properly blinded, provides a more reliable assignment of cause and lessens the probability of information bias. Using risk factors measured at entry into the study, the authors performed a Cox regression analysis to identify significant factors which predict mortality from coronary heart disease. This analysis identified age, blood pressure, forced expiratory volume, and serum cholesterol as statistically significant risks. Smoking was not found to be a significant factor.

Similar findings were reported by the Oslo Study Group on their intervention trial on diet and smoking (Hjermann 1981). This study involved 1,232 healthy men who smoked, had high blood pressure, and had high serum cholesterol levels. The men were randomly

allocated to an intervention or to a normal care group, and were followed for five years. During the trial, the mean tobacco consumption per man decreased by 45% more in the intervention group than in the control group. However, the reduction in CHD incidence in the intervention group was significantly correlated only with initial serum cholesterol levels and with the change in serum cholesterol. The authors stated that "it is possible that observational studies have overestimated the decline in risk of CHD brought about by reducing cigarette consumption." One might also attribute the surprising finding to insufficient statistical power to detect a risk reduction due to smoking intervention, to a non-reversible triggering mechanism involved with smoking, to intervention only being effective when tobacco consumption is reduced to zero, or perhaps as likely, to unknown confounding factors which are associated with or predispose persons to smoke and develop coronary heart disease.

In addition to smoking, the Framingham study has also established the other well-known major risk factors for CHD, namely hypertension and hyperlipidemia. Some other risk factors, such as personality type and family history of early cardiovascular disease,

also have been identified, but the three major ones have received most attention with regard to their potential for modification and subsequent reduction of CHD risk. This strategy has been the focus of several large trials over the past fifteen years which have sought to more precisely define the factors which increase the risk of CHD, and demonstrate that their reduction leads to reduced risk of mortality from CHD. Although the intervention trial as an epidemiologic approach, particularly when applied to large populations in different settings, should produce explicit findings regarding the importance of specific "risk factors" for CHD, the actual results are far from being definitive. They certainly leave open the question of how much CHD may be due to cigarette smoking.

If a factor or group of factors increase the risk of mortality from coronary heart disease, then (unless there is an irreversible threshold) the removal or reduction of that factor or factors should result in reduction of risk. This was the premise behind the Multiple Risk Factor Intervention Trial (MRFIT). Beginning in 1972, 22 clinical centers throughout the United States examined 361,662 male volunteers between the ages of 35-57 for presence of the three factors

(elevated serum cholesterol, elevated blood pressure, and cigarette smoking) considered to increase risk of CHD (MRFIT Research Group 1982). 12,866 men, identified as being at highest risk, and agreeing to participate in a long-term study, were randomly allocated to a special intervention group for treatment of high blood pressure, counseling to reduce smoking, and advice on diet to reduce serum cholesterol; or to a control group with their usual sources of medical care. The groups were followed for an average of seven years, and both demonstrated a reduction in risk factor levels. Yet, annual mortality from CHD was 17.9 per 100,000 population in the intervention group compared to 19.3 in the usual care group, a statistically non-significant difference of 7.1%. Total mortality in fact, was higher in the intervention group. The smoking cessation program was particularly successful; the proportion of smokers in the special intervention group declining from 63.8% to 32.3%. However, the proportion of smokers in usual care group also decreased, from 63.5% to 45.6%. The usual care group demonstrated a reduction in each of the "risk factors" for which they (and the intervention group) were initially selected. Thus, despite 29% fewer smokers in the intervention group, only a small, non-significant

difference in CHD mortality between the groups was found. This finding could reasonably be considered to indicate that cigarette smoking is not a major CHD risk factor, although many other explanations for the lack of a significant reduction in mortality among men in the intervention group have been suggested. The statistical power of the study could not show an observed 7% difference to be statistically significant, but were it large enough to show significance at that level of effect, smoking could not have accounted for much excess risk, given the other, more important CHD risk factors.

According to Werko (1987), the study was impossible to interpret because the statistical power calculations and the resultant sample size were determined from Framingham data which reflect entirely different study conditions, and the study took place at a time when CHD rates were rapidly declining. The authors of the study dismissed two reasons for the negative findings (i.e. the intervention program was without benefit, or the program was beneficial but not observable), and instead suggested that one or more parts of the intervention program had an unfavorable effect on mortality in some

subjects which offset the beneficial effect in others (MRFIT Research Group 1982). Stallones (1983), however, rejected these explanations, and concluded instead that "....the best explanation for the failure to detect a beneficial effect in MRFIT is that no benefits accrued."

These findings might not be considered relevant, given the prior scientific data which previously had showing that smoking, hypertension, and high serum cholesterol were significant risk factors. However, other intervention studies arrived at similar conclusions. The Multifactor Primary Prevention Trial in Goteborg, Sweden (GPPT) started before MRFIT, ran for a longer period of time, and was population-based rather than focused on a largely self-selected, high-risk population (Wilhelmsen 1986a,b). All males living in the city of Goteborg and born between 1915-1922 or 1924-1925 were invited to participate. One-third (10,004) were randomly assigned to an intervention group and the other two-thirds acted as controls. Risk factor status of the entire intervention group was determined, but only for a 2% sample of the controls, to avoid the potential ethical problem of not treating all persons at high risk. The intervention strategy was similar to that used in MRFIT. Four years

after entry into the study, the levels of risk factors were determined again for the entire intervention group and a sample of the controls. Six years later, new 20% samples of the intervention and control groups were re-examined. Both groups demonstrated a decrease in all three risk factors. There was no effect of intervention on CHD morbidity or mortality, despite a 2.9% greater drop in the percentage of smokers in the intervention group compared to the control group. Interpretation of this study is difficult because 25% of the potential intervention group refused to participate and had three times the mortality of those who did (with risk factor levels never being determined).

The WHO European Collaborative Trial was designed to avoid the contamination of control subjects by risk reduction strategies used on the intervention group. This was accomplished by using factories as the recruitment units, and allocating one of each matched factory pair to either the intervention group or to the control group. Half received advice on dietary lowering of cholesterol level, control of smoking, overweight, and blood pressure. Ten percent of the half not receiving advice were screened at entry and during the trial to

determine their risk factor level. The trial comprised working populations (in factories) in the United Kingdom, Belgium, Spain, Italy, and Poland, although only the data from the first two countries were actually analyzed in depth. (WHO 1983) In the United Kingdom, 18,210 men took part, although cigarette smoking was the only risk factor which intervention reduced. (Rose 1983) Over the whole trial, ten percent of the high risk men quit smoking, four percent of the entire cohort quit. Fatal coronary heart disease was 8% more frequent in the intervention group, while mortality from all causes was 11% higher in this group. In addition, strokes and cancer deaths were slightly more frequent in the intervention group. In contrast, results from the Belgian portion of the study were in the opposite direction (Kornitzer 1983). Among the 19,049 men who participated, total mortality was significantly lower in the intervention group, as was the frequency of myocardial infarction. Although coronary mortality was lower in the intervention than in the control group, the difference was not statistically significant.

In all five countries, a total of 60,881 males, ages 40-59 entered the trial. The final results of the study indicated a reduction of 6.9% in

fatal coronary heart disease in the intervention group and a reduction of 10.2% in total CHD, although neither difference reached statistical significance (WHO 1986). The validity of these results is questionable, since the study involved only working men, some of whom refused to participate, and 10% of the control groups were missing from the published analysis. Although the authors of the study concluded that the benefit was significantly related to risk factor change, Werko (1987) questioned the accuracy of the data presentation in the report, and commented that the authors "are not prepared to accept inconclusive results." Rather, he chides, "....sophisticated statistical calculations are instead used to create some support for the preconceived ideas behind the trial."

A small intervention trial on 1,445 cigarette smokers with the highest risk of coronary heart disease (and chronic bronchitis) found no significant difference between the normal care and smoking intervention groups in probability of death from coronary heart disease during 7-9 years of follow-up (Rose 1978, 1982). In fact, although "smoking is the most investigated risk factor in terms of its biological effects, no prospective population study has established

which biological measurements account for the excess coronary risk related to smoking" (Salonen 1988).

Thus, reductions in the three "major" risk factors identified in the Framingham study failed in three large and one smaller intervention trials to lower the risk of coronary heart disease demonstrably.

Why then do retrospective and prospective non-intervention studies indicate an important role for hypertension, hyperlipidemia, and cigarette smoking in the development of CHD? There may be a risk associated with these factors, but the degree of risk is different for each, and their separate effects are impossible to tease out from intervention trials which may not reduce the level of one factor while holding the others constant. However, even within a single factor, there is substantial variation by gender and specific manifestation of CHD. For example, smoking appears to be a significant predictor of sudden death in males, but not females, and makes no significant contribution to the risk of angina pectoris (Schatzkin 1984, Stokes

1987). Similarly, serum cholesterol is insignificant for those over 64, as is cigarette smoking.

The effect on CHD risk of coffee drinking, a habit closely correlated with cigarette smoking, remains controversial despite several large studies. A 19-year prospective investigation of over 2,000 men employed by the Chicago Western Electric Company found increased mortality from coronary heart disease among men drinking 6 or more cups of coffee per day (LeGrady 1987). The risk was present in both smokers and non-smokers, indicating its independence. Interestingly, the risk due to this level of coffee consumption was higher in the non-smokers than in the smokers. However, dietary fat intake was not adequately assessed by the 24-hour recall method used in the study and it failed to find an association between serum cholesterol and coffee drinking. A recent Danish study (Pietinen 1988), in contrast, found that moderate coffee drinking raises serum cholesterol in men. These results are not consistent with the previous literature nor with more recent studies; Stone (1987) cites a variety of studies on this topic with a variety of results. He concludes that "the evidence does not support a significant, independent

relationship...". Shirlow, et al (1988) measured the blood pressures of some 5,000 Australian volunteers. They found that average caffeine consumption per day was not associated with high blood pressure after controlling for time since last caffeine consumption. Perhaps, coffee drinking is merely an indicator a particular lifestyle which is associated with high CHD risk. Recent results from Norway (Jacobsen 1987) suggest that this may be so. Although this study was cross-sectional and whether a subject drank coffee or had other risk factors may have been affected by knowledge of his disease status (e.g. a diagnosed CHD patient may have quit drinking coffee), the study appears to indicate an inverse correlation between coffee drinking and generally recognized "healthful" behaviors. These behaviors include use of fruits and vegetables, preference for low-fat milk, physical activity, and consumption of table fat containing high amounts of polyunsaturated fatty acids.

Thus, the CHD risk picture is very complex, and the failure of intervention indicates that other factors intimately associated with the three major risk factors, but not controllable through intervention on the factors (i.e. confounders), explain at least part of the

apparently increased risk which has been associated with smoking, diet, and high blood pressure. Among these are genetic, immunological, psychological, anatomic, and endocrinological factors, as well as environmental influences such as electrolytes in drinking water (Punsar 1975, Salonen 1988).

HYPERTENSION

Of the three identified "classic" risk factors, hypertension is most readily treatable, and there is substantial documentation that its treatment reduces the risk of cardiovascular mortality (Garrison 1987).

Hypertension is related to obesity, and several studies have shown obesity to be associated with increased mortality from CHD. A recent Finnish study confirmed that a high body mass index is a significant predictor of acute myocardial infarction among men (Tuomilehto 1987). It should be noted that the other extreme of body mass or weight also is associated with increased risk of mortality. Although it has been suggested based on reanalysis of Framingham data (Garrison 1983), that this excess is due to a disproportionate number of smokers in the lower weight groups, Vandebroucke, et al (1984) found that smoking did not explain the higher mortality among persons with lower weight in a 25-year prospective follow-up study.

In addition to cardiovascular disease, other conditions such as diabetes and gall bladder disease occur more frequently among overweight persons (Simopoulos 1985). Stallones (1985) discusses ten reports of mortality from all causes combined, of which five showed higher death rates only at the upper extreme of body weight, and two demonstrated a monotonic increase in mortality with increasing weight. In a review of the health implications of overweight and obesity, Simopoulos (1985) notes that several recent reports indicate that even mild degrees of overweight are a public health problem. Furthermore, there is a progressive increase in both mortality and morbidity associated with increasing weight, and the extra risks due even to slight weight excesses are particularly important for persons with pre-existing risk factors such as hypertension. In fact, Manson, et al (1987) have shown that previous studies have systematically underestimated that impact of obesity on premature mortality.

Numerous studies have shown that smokers weigh less than non-smokers, and that smoking cessation leads to weight gain (Waack 1982, Emont 1987). For example, Coates and Li (1983) followed 373

asbestos-exposed workers who had participated in a smoking cessation program. Though the sample was small, the results clearly indicated that persons who quit smoking for one year showed significantly greater weight gain than those who continued smoking. The reason for this phenomenon, and its basis in nicotine pharmacology have been recognized only recently. The Zutphen Study, in which a random sample of middle aged men has been followed prospectively since 1960, found physical activity and cigarette smoking to be the important determinants of body fatness (Kromhout 1988). The authors of this study suggest that this may be due to enhanced thermogenesis, particularly in leaner men, related to smoking and mediated by the sympathetic nervous system. Hofstetter, et al (1986) studied the metabolic effects of smoking among eight healthy cigarette smokers. 24-hour energy expenditure, with and without smoking, was measured by calorimetry in a respiration chamber. The study found that cigarette smoking increased 24-hour energy expenditure by about 10%. However, this appears not to be the only mechanism by which smoking helps weight control.

Grunberg (1982) compared taste judgement among smokers allowed to smoke, smokers not smoking, and non-smokers. He performed a complementary experimental study using male rats that were administered nicotine subcutaneously. Grunberg found that in humans, smokers who were allowed to smoke ate significantly less sweets than non-smokers or than smokers not allowed to smoke; the latter expressing the greatest preference for sweet foods. Similarly, animals receiving nicotine significantly decreased their consumption of sugar solution during nicotine administration, but did not alter their consumption of bland laboratory chow. Average body weight showed an inverse dose-response relationship to amount of nicotine administered. Further studies (Grunberg 1985) demonstrated that the effect of nicotine on selective consumption of foods related both to sweet taste and caloric content, although the former was particularly important. An additional comparison of per capita cigarette and sugar consumption in the U.S. from 1964-1977 indicated a significant inverse relationship (Grunberg 1986). However, because the changing age structure of this country, and other potentially confounding factors were not taken into account in this comparison, this evidence is somewhat unpersuasive.

The importance of weight gain avoidance as a factor in continued usage of cigarettes appears to differ between males and females. In order to eliminate the human sociological reasons for such avoidance behavior, Grunberg, et al (1986) studied the effects of nicotine on body weight and food consumption in female rats. Previous studies have shown that this animal model was consistent with results in humans. Control animals given saline gained significantly more weight than animals on three different levels of nicotine. A dose-response relationship was evident, with the intermediate and low nicotine groups also gaining significantly more weight than the high nicotine group. After drug administration ceased, the body weights of all four groups were similar. Foods consumption patterns were slightly different. The control group consumed slightly more food during drug administration, but the two lower nicotine groups increased consumption even more. The group on the highest level of nicotine, however, decreased consumption significantly compared to the other nicotine groups. Following cessation of the drug, all nicotine groups increased food consumption compared to controls, significantly so for the highest nicotine group. Estrous cycle had no

effect on food consumption. Comparison of these results with previous studies of male rats under identical conditions revealed that similar doses had a greater effect on females than on males. Furthermore, after cessation of nicotine administration, females with access to bland food and water gained significantly more weight than controls, while males did not.

Hypertension is associated with heavy alcohol consumption (Trevison 1987) and _____ has been shown experimentally to cause epicardial coronary artery vasoconstriction (Hayes 1988). The etiology of essential hypertension is multifactorial, through embodying a variety of factors such as poor socioeconomic conditions and low IQ (Lindgarde 1987), and suppression of anger (Johnson 1987). A study of the incidence and precursors of hypertension in offspring of the original Framingham cohort indicated that adiposity, heart rate, and triglyceride level were significant independent predictors of hypertension in males, as were adiposity, heart rate, hematocrit, and alcohol consumption in females (Garrison 1987). Consumption of alcohol appeared to be associated with rapid onset of hypertension. The study's authors suggested that weight control

deserves the highest priority in efforts to prevent hypertension in the general population. The effect of cigarette smoking on hypertension, however, is equivocal. Several reports demonstrate that smoking produces an acute rise in blood pressure, but others show that smokers have lower average blood pressure than non-smokers. Furthermore, although hypertension is a powerful risk factor for stroke, the Gotborg study (Welin 1987) found smoking not to be a significant risk factor. Population surveys demonstrate that smokers generally weigh less than non-smokers (Albanes 1987), and Schoenenberger and others have shown that reduced blood pressure among smokers is related to their lower weight (Schoenenberger 1982, Greene 1977, Tuomilehto 1986).

However, Green, et al (1987), in an epidemiologic study of the association between smoking and blood pressure in a working population, found an inverse association between smoking and blood pressure which was not due to smokers' lower weight. (Green 1987) The study was carried out in two phases between 1979 and 1984, and initially included a total of 2,781 males and 461 females, of whom 436 males and 64 females were excluded because of pre-existing heart

disease or hypertension, or because they were on medication for treatment of hypertension. While the mean blood pressure differences between smokers and non-smokers were not large, they were significant. No dose-response relationship was demonstrated. Adjustment for possible confounding by age, coffee consumption, etc. did not change the inverse association. However, no information on dietary habits was obtained, although given the higher alcohol intake of smokers and the custom of consuming sodium-rich snack foods with alcohol, control for this potential confounder probably would have enhanced the negative association. The authors suggest that smoking might have a stress-reducing effect with consequent lowering of blood pressure.

The Caerphilly Heart Study is an ongoing prospective study of men aged 45-59 living in South Wales (Elliot 1987). In the initial screening, cross-sectional analyses of the prevalence of hypertension and various risk factors found higher blood pressures in lifelong non-smokers than in current smokers; the difference being significant for diastolic blood pressure. Ex-smokers were intermediate. Alcohol usage, in contrast, was found to be significantly positively related to

diastolic and systolic blood pressure. Body mass index (BMI) was also found to be significant, and the joint effect of alcohol and BMI were additive. The authors found little evidence for an association between diet and blood pressure.

HYPERLIPIDEMIA

The role of the other identified major risk factor, hyperlipidemia, is substantially more complicated, and is indicative of the climate in which targets for preventive measures are identified without proper scientific evidence. It is generally accepted, based on epidemiologic, experimental, and clinical evidence, that there is a reasonably strong, consistent relationship between blood lipoproteins, atherosclerosis and CHD risk (Blackburn 1986). The average levels and distributions of total serum cholesterol and other blood lipids vary widely among populations, and associations in populations are strong between mean level of total serum cholesterol and CHD incidence. However, rarely is the distinction made between serum and dietary cholesterol, despite agreement that elevation of the former is a risk factor (although there is disagreement about the threshold for increased risk), and controversy over the effect of diet, in general, and dietary cholesterol in particular (Kritchevsky 1987, Thompson 1987).

A prospective investigation, the Ireland-Boston-Diet-Heart Study (Kushi 1985), followed three cohorts of men. These included 563 men ages 30-69 living in Boston who had emigrated from Ireland, 572 brothers of these men who remained in Ireland, and 373 men who were born and lived in the Boston area and whose parents both emigrated from Ireland. Baseline examinations were conducted, and dietary habits were ascertained using the diet-history method. Follow-up over 17-23 years for mortality from coronary or ischemic heart disease resulted in 93% successful with vital status ascertainment 148 deaths from these causes. Mortality rates did not differ significantly among the three cohorts, although the Boston brothers had significantly higher systolic blood pressure and percentage of cigarette smokers. Serum and dietary cholesterol levels were also higher in this group, although not significantly so. Although these results demonstrate the weakness of the hypotheses linking diet and smoking to CHD mortality, they reflect the risk factor status of each subject at the start of a study which lasted about 20 years. The statistical associations found in this study may not, therefore, be valid measures of the actual exposure/disease associations in this population. Descriptive data on international

variations similarly spotlight the nonuniformity of the heart disease/cholesterol association. For example, France has the ninth highest cholesterol intake of some 24 countries plotted by Conner and Conner (1986), but ranks twentieth in coronary mortality rate; Finland's intake is less, but the country ranks second; Israel and Sweden are equally anomalous. One complicating factor is the difference between the risks associated with different lipoprotein patterns, e.g. Low Density Lipoprotein cholesterol (LDL) associated with increased risk of cardiovascular disease, while reduced risk is associated with the High Density (HDL) variety. (Another is that levels of HDL appear to be reduced by smoking (Criqui 1980), but this effect is mainly upon the HDL_3 subfraction (Haffner 1982), which is considered to be unrelated to coronary heart disease.) Furthermore, lipoprotein patterns show distinct genetic heritability (Austin 1987) and there is substantial correlation between their levels and other CHD risk factors (Criqui 1986). Even this correlation is not clearcut. Rabkin, et al (1981) found that weight loss was not correlated with changes in serum HDL cholesterol in men or in women who were non-smokers. However, among female smokers, even a moderate weight loss was associated with a significant increase in serum HDL

cholesterol concentration. Alcohol seems to raise HDL cholesterol and lower LDL cholesterol, while cigarette smoking apparently has an opposite effect. The practical importance of these observations is dubious, however, since Criqui, et al (1987) have found that the effect of alcohol consumption on cardiovascular disease mortality is, for the most part, independent of a cholesterol pathway, and the apparent effect of smoking is totally independent. Salonen, et al (1987) suggest that the HDL-elevating effect of alcohol, however, is greater in smokers than in non-smokers, and recent results from a prospective study in Finland (Suhonen 1987) demonstrate a deleterious effect of alcohol consumption, even at moderate levels, on the incidence of sudden cardiac death, particularly among non-smokers.

Given the largely negative results of intervention trials discussed previously and the complicated role of diet in determining serum lipid levels, it is no wonder that Werko (1987) decries the "...aggressive marketing of the lipid hypothesis with its emphasis of dietary change.....". The same type of marketing is likely to underlie the cigarette hypothesis, which to some degree draws upon the early MRFIT finding of reduced serum total cholesterol in men who quit

smoking compared to those who did not. Schoenenberger (1982) explains this finding by noting that people who quit might be more compliant both with efforts to cease smoking and with adoption of other "healthier" lifestyles.

Tuomilehto, et al's (1986) findings provide evidence favoring Schoenenberger's explanation. This, in turn, may indicate that at least some of the positive CHD association with smoking results from uncontrolled confounding related to intrinsic differences between smokers and non-smokers (which are not affected by smoking cessation programs or other intervention techniques).

GENETIC DETERMINANTS

The intrinsic differences between smokers and non-smokers are most apparent in readily observable constitutional characteristics such as personality, but also exist in the direct or indirect genetic influences which dictate a person's predisposition to CHD, likelihood of being a smoker, and the levels of other risk factors. A genetic component of CHD has been known for 40 years, beginning with the recognition of aggregation of the disease in families (Berg 1983). Results from the prospective British Regional Heart Study of 7,735 men aged 49-59 clearly indicate that increased risk of heart attack is strongly associated with a parental history of ischemic heart disease, and that only a small proportion of this excess risk can be attributed to increased levels of the "principal risk factors" for the disease (Phillips 1988). Although one might attribute disease concordance in families to an expected clustering of environmental or behavioral risk factors, Khoury, et al (1988) have demonstrated mathematically that for diseases exhibiting familial aggregation, genetic factors are of greater importance.

Numerous studies, including several of CHD concordance in twins, conducted since the early reports of these clusters confirm the high excess risk associated with a family history of CHD. In a comprehensive review on genetics in CHD, Robertson (1987) discusses many of these studies, and categorizes the evidence of a genetic component in CHD into three types. The first type is results from studies which indicate clustering of the disease in families, without reference to the cause of the disease. The second type refers to the occurrence of a particular lipid profile due to inheritance of a single gene. The third type refers to evidence of heritable polygenic variation such as total serum cholesterol. A good example of the second type of evidence is familial hypercholesterolemia, which has long been recognized as being simply inherited. Persons homozygous for the gene, which through a complex pathway controls cholesterol synthesis, demonstrate extraordinarily high concentrations of serum cholesterol and experience early coronary death. Heterozygotes also manifest high serum cholesterol levels and increased CHD risk, but to a lesser degree. Robertson presents evidence from other studies which indicate other monogenic variants affecting serum lipids. He cites several studies which demonstrate a

genetic contribution to total serum cholesterol and triglyceride variation among individuals, as well as to HDL concentration. One constituent of serum lipoproteins, Apo-E, mediates high-affinity binding to the low density lipoprotein reception (Mahley 1988). A mutant form of Apo-E, defective in this binding ability, is associated with a genetic disorder involving elevated levels of cholesterol in plasma and accelerated coronary artery disease.

Recently, Simons, et al (1988) evaluated plasma lipid levels among a random sample of Jerusalem adults. Family history of CHD, extant CHD, and information on several risk factors was determined with the standardized protocol of the Lipid Research Clinics. Twelve percent of the subjects had coronary heart disease, and twenty percent had a family history of CHD. Compared to subjects with CHD, HDL concentration was lower in subjects having both CHD and a family history of heart attack. No risk factor, other than lower HDL concentration, predicted the occurrence of CHD in those with a positive family history. An overall logistic model found that the significant predictors of CHD were age, total plasma cholesterol, hypertension, family history, and HDL level. Odds ratios for

cigarette smoking were not significant; 0.52 (0.21-1.25) for those with a positive family history, and 0.72 (0.44-1.18) among those without. However, these results, as well as those regarding HDL, must be viewed cautiously since this study was cross-sectional and subject to selective survival, changed behavior (e.g. persons with CHD might have been more likely than persons without CHD to quit smoking), and reporting bias. Furthermore, the family history information was not validated. Nevertheless, this study supports the hypothesis that reduced HDL concentration might partially explain the aggregation of coronary heart disease in families.

There is evidence from studies of twin pairs that levels of serum apoproteins and cholesterol concentrations are affected by lifestyle factors (Hayakawa 1987). Thus, these lifestyle factors, which would tend to cluster in families, or mutual environmental exposures may affect other risk factors in families, and thereby, mimic a genetic component of CHD. However, ten Kate, et al (1982) have shown that familial aggregation of coronary heart disease cannot be entirely explained by the familial clustering of known CHD risk factors. In their case-control study of myocardial infarction survivors, life table

regression analyses using the "classic risk factors" (serum cholesterol, triglyceride and fasting blood glucose levels, blood pressure, and cigarette smoking) were unable to predict family occurrence of disease. The genetic component of CHD, therefore may originate largely in genetic factors. One possibility is impaired fibrinolysis resulting in increased plasma fibrinogen (Francis 1988). However, while the evidence for a genetic component in CHD is compelling, the magnitude of the genetic contribution to CHD is immeasurable in the maze of risk factor inter-relationships, and our lack of knowledge regarding lipoprotein metabolism, atherosclerotic plaque formation, and the extent to which individuals respond differently to environmental influences.

The pattern of morbidity and mortality changes in this century is due to ecologic, environmental and/or nutritional factors. This pattern cannot be accounted for by changes in the genetic structure of a population because significant changes in gene frequencies require several generations (Berg 1983). However, these environmental changes may reasonably be assumed to act to cause CHD in persons with a genetic predisposition to the disease. If this predisposition is

linked directly or indirectly with a predisposition to become a smoker, it would partially explain the discrepancy between results from intervention trials and other epidemiologic investigations. For example, in persons strongly genetically predisposed to hypertension, "there is substantial evidence incriminating environmental co-factors such as high salt intake and low potassium intake, obesity, and alcohol" (Kannel 1987). Certainly, the likelihood of being a smoker is strongly associated with the likelihood of using alcohol.

The effect of co-factors linkage is apparent in the various psychosocial factors, chronic and acute stress-induced levels of physiologic reactivity, and the biobehavioral mechanisms which affect risk of CHD (Shepherd 1987, House 1988). Type A behavior and other psychosocial factors such as worries about age and personal matters, work overload, marital disagreements, and difficulty falling asleep, were found in the Framingham study to be associated with CHD incidence (Haynes 1980, 1983, Eaker 1983). Although recent evidence from the Western Collaborative Group Study (Ragland 1988) indicates a protective effect of Type A behavior on subsequent coronary heart disease mortality among patients surviving an initial coronary event, Framingham men exhibiting Type A behavior, characterized by aggressiveness, competitiveness, time urgency, etc., had more than a twofold increased CHD risk. Both housewives and women working outside the home who demonstrated Type A personalities had increased risk of coronary heart disease. Men married to women with at least thirteen years of education were significantly more likely than men married to women with a

grammar school education to develop CHD (Haynes 1983). While men married to women who worked outside of the home had incidence rates similar to those married to housewives, men who were married to women with white-collar jobs had a statistically significantly elevated relative risk compared to those married to clerical workers, blue-collar workers, or housewives.

Other personality types have also been shown to be at higher risk of CHD. Barefoot, et al (1987) found suspiciousness, hostility, cynicism, etc. to be directly predictive of mortality during a 20-year follow-up. Most deaths in this cohort were due to CHD, although the association of the hostility factor was not assessed with individual causes-of-death. In a study of Finnish men aged 40-59, Koshenvuo, et al (1988) found that hostility was a strong determinant of coronary attack among those with previous ischemic heart disease and hypertension. Wielgosz, et al (1988) similarly found that hostility was a risk factor for myocardial infarction, particularly if the hostility was suppressed. This Canadian study also determined that inadequate relaxation was an independent risk factor for MI. Grossarth-Maticek, et al (1985) prospectively studied 1,353 residents of Crvenka,

Yugoslavia. Not only did they find a fourfold excess risk among subjects with high scores for rationality/anti-emotionality (a factor related to suppression of aggression), analysis of the inter-relationship of this factor with smoking revealed that the apparent positive relationship with the latter disappeared with analytic control for the former. Thus, differences in CHD mortality between smokers and non-smokers were explained entirely by this psychosocial factor differences.

Not being married, having low income, and having little education are related to higher risk of CHD (Salonen 1987). Kosken, et al (1979) found that unmarried men and women have higher mortality from cardiovascular disease than do married ones. More recently, in a study utilizing that pooled data from two large population-based studies, separated or divorced persons had the highest hospitalization rates for heart attack or stroke (Ventners 1986). This same group reported higher levels of alcohol use and smoking. In fact, the study also found significant differences in levels of serum cholesterol, education, drinking, physical and leisure time activities among different marital status groups.

The MRFIT data showed that activity during leisure time was inversely related to smoking behavior and to the risk of CHD mortality (Leon 1987). Marti, et al (1987) demonstrated a similar, though weaker relationship to CHD risk factors in Finnish women.

More recently, Salonen, et al (1988) used six-year follow-up data from two Finnish cohorts to demonstrate that persons who were comparatively sedentary in their leisure time and work activities had significantly higher risk of ischemic heart disease than did those who were not. Of particular importance was the finding that the physically inactive persons were more often smokers than were the more active ones. Thus, any excess cardiovascular disease risk due to physical inactivity might be falsely attributed to cigarette smoking if the former is not accommodated in a particular study. Salonen, et al (1981) have noted that other potentially unhealthy behaviors tend to cluster similarly, thus increasing the chances that spurious risk estimates will be associated with smoking.

These activities, marital status, and other social or psychological support systems or mechanisms can mediate the effect on CHD risk of other social stressors. While a substantial amount of research demonstrating increased risk of cardiovascular disease associated with the number and severity of life changes or significant life events has been published (Rahe 1987), it also has been recognized that "resistance factors" or coping mechanisms may effectively buffer the response of humans to stressors (Chesney 1982). A recent prospective study of Swedish males followed for nine years (Welin 1985) clearly demonstrated a significant relationship between lack of social activities and 3-4 times the CHD of men participating in various activities.

Another recent Swedish study examined the relationship between cardiovascular mortality and social interaction in a six-year follow-up of a random population sample (Orth-Gomer 1987). The investigation used data from the Swedish National Survey of Living Conditions, which was designed to describe the social well-being of the population in terms other than economic conditions. Data on mortality were obtained from the Swedish National Mortality

Register. Over the six-year follow-up period, 414 deaths from cardiovascular disease occurred among the study sample of over 17,000 men and women. Comparisons of mortality among tertiles of the social interaction network scores, controlling for potential confounding, revealed a statistically significantly elevated risk of 1.46 (1.12-1.73) for the lower tertile compared to the upper two. The same set of psychosocial factors are important in determining survival after an initial myocardial infarction (MI), as well. A study of 2,320 male MI survivors, followed for three years, demonstrated a significantly increased risk of death associated with high stress levels and social isolation (Rubermen 1984).

Several other psychosocial factors have been shown to affect the risk of cardiovascular mortality. Work-related stress in different forms and among different occupations has been shown to increase the risk of cardiovascular disease. Netterstrom, et al (1988) attribute their finding of increased MI risk among urban bus drivers in Denmark to the drivers' "increased work pace" and mental burden due to driving in heavy traffic. In Sweden, surgeons appear to be at higher risk of cardiovascular mortality than do other physicians or other

professions (Arnetz 1988). In a study of a small random sample of surgeons and general practitioners, Arnetz, et al (1988) found that overall mental strain was greater among surgeons, and that they reported less ability to relax after work. Other work environments with excessive psychological demands and little intellectual demands and those characterized as "hectic without the possibility of learning new things" have been found to double the risk of cardiovascular disease in several studies (Theorell 1984). To some extent, these findings are due to self-selection into these occupations and to somewhat distorted descriptions given by respondents of their work environments, but the evidence for a positive association is strong. In addition, Theorell, et al (1984) demonstrate that purported CHD risk factors such as smoking and high blood pressure also may be influenced by psychosocial factors. The direction of this association may not be consistent, however. A cross-sectional survey of active-duty Air Force personnel, which found psychological well-being to be associated with "positive" health practices such as adequate rest, eating breakfast, and exercising sufficiently, also found a positive association with cigarette smoking (Wetzler 1988).

CONCLUSIONS

While the mechanism for stress-induced CHD, or that due to other psychosocial factors is evident, there is little documented experimental evidence of mechanisms involving tobacco smoking (Blackburn 1986). Furthermore, recent evidence demonstrates that among patients with ischemic heart disease, cigarette smoking does not appear to immediately increase the frequency or severity of ventricular arrhythmia (Myers 1988). Nor does it acutely raise blood pressure, plasma catecholamines, or heart rate. This is not surprising when one examines the epidemiologic literature linking tobacco usage to cardiovascular disease.

In considering the criteria for causality invoked by epidemiologists, as described earlier, to the smoking/CVD association, it can be seen that the causal link is not as evident, particularly in comparison to other factors, as generally believed. When based on Framingham data, the association conveys "strength" in terms of a risk estimate, and the correct temporal sequence, but intervention trials suggest negligible strength and much inconsistency. There is not evidence of

specificity, and only speculation about a biological mechanism for the link. In contrast, applying these criteria to the other identified risk factors vaults them into etiological prominence.

If, based on the results of intervention trials, there is a propensity to diminish the significance of cigarette smoking as an etiological factor, the finding of the association in other study designs must still be accounted for. Clearly, one explanation is that unknown or unmeasured factors confound the association, and most likely among these is the evidence that smokers independently segregate for CVD susceptibility. An intervention strategy aimed at smoking cessation might reduce that exposure, but would have no effect on the underlying (unknown) risk factors with which it is correlated. Thus, the intervention will be without effect, despite the indication from other studies that it should result in lowered risk. The intervention trial, properly done, is the strongest design epidemiology offers for "proving" causality. Several intervention trials among different populations with similar, negative results are persuasive evidence against a causal association. Therefore, it is an inescapable

conclusion that estimates of the risk of CVD due to cigarette smoking must be critically reconsidered, and in all likelihood reduced.

LUNG DISEASES

LUNG CANCER

An apparent role for cigarette smoking as a risk factor for lung cancer emerges from many studies. Yet, the emotional and political forces affecting the perception of this role by the public and scientific community have tended to distort the interpretation of the existing scientific evidence regarding the justification or the magnitude of lung cancer risk which might be attributable to smoking. Well-documented information about a multitude of other lung cancer risk factors such as urbanization, social class, religion, ethnicity, occupational exposures, asbestos, SO_2, arsenic, radon, polycyclic hydrocarbons, chloromethyl ethers, chromium, nickel, air pollution, ionizing radiation, nutritional status, and genetics seems to have been lost to common knowledge. Recently, Wynder and Corey pointed out that, "....the dominance of cigarette smoking as a risk factor has led to a focus on this variable to the relative neglect of other factors." (Wynder 1987)

Inconsistencies between descriptive data on smoking habits and on the occurrence of lung cancer in populations abound, and the unwillingness to confront these anomalies is somewhat suspect. For example, there are several types of lung cancer with somewhat different etiologies; adenocarcinoma of the lung, a cell type less strongly related to smoking, accounts for 33-35% of the lung cancers in this country (Mathay 1987). Yet, recent government pronouncements (U.S. DHHS 1987) claim that smoking is responsible for 75-80% of lung cancer deaths. Furthermore, there has not been an increase in the proportions of various cell types associated with smoking even though lung cancer incidence has increased in females, reputedly as a consequence of smoking (Beamis 1975). The observed shift in the relative proportions of different cell types may actually indicate a causal role for a non-cigarette-linked factor that is more common in women (Wynder 1987). Gillis, et al (1988a) investigated the smoking/lung cancer relationship in Glasgow and the West of Scotland, an area with the highest recorded incidence of the disease in the world. In this case-control study they found lower relative risks at all levels of smoking than those in the published literature. Furthermore, they found a significantly elevated relative

risk only for those who smoked less than a pack per day. Among those who smoked more than 20 cigarettes per day, the relative risk did not rise significantly. A cohort study (Gillis 1988b) which attempted to explain these findings found no obvious reasons, and merely confirmed the case-control results.

Descriptive epidemiologic data from other countries provide further evidence of these inconsistencies: Belcher (1987) has demonstrated that the incidence of bronchial carcinoma has declined in the group of British women who had higher per capita lifetime consumption of cigarettes than any previous group of women. Time trends in lung cancer incidence data collected by the Cali, Colombia cancer registry reveal a constant proportion of adenocarcinoma among females during the last 15 years, despite the adoption of cigarette smoking by women at younger ages after World War II (Cuello 1983). Also, a predicted large rise in lung cancer among males due to increasing cigarette use and a shift from dark to light tobacco (which makes inhalation easier) has not occurred. Cigarette smoking data from Italy fail to account for the rise in lung cancer mortality in that country, and "may indicate the operation of some general

environmental agent(s)....." (Saracci 1987). Kurihara (1987), Tsai (1988), and Mori et al, (1984) report similar observations regarding lung cancer mortality in Japan, Taiwan and Hong Kong, respectively. Gao, et al (1988) reported that "smoking is not responsible for the high rates of aclenocarcinoma among females in Shanghai. In addition, the differences in lung cancer incidence between whites and nonwhites, and by geography cannot be explained only by differences in smoking (Blot 1982).

Clearly, the nature of the cigarette/lung cancer association is not as simple as usually portrayed. In this chapter, the role of other factors as recognized causes of lung cancer and as modifiers or determinants of the risk associated with cigarette smoking will be discussed in the context of the often overlooked multifactorial etiology of this disease.

GENETIC DETERMINANTS

Lung cancer is not an inevitable consequence of cigarette smoking. Thus, host factors, some which may be genetically determined, influence susceptibility of lung cancer. The same factors might also help determine whether an individual becomes a smoker. Familial occurrence of lung cancer is somewhat rare, though anecdotal reports appear regularly in the scientific literature (Li 1988). For example, Paul, et al (1987) recently reported about three brothers with alveolar cell carinoma which occurred when each reached approximately the same age.

Actually the first published epidemiologic evidence about genetic factors in the etiology of lung cancer appeared over twenty years ago (Tokuhata 1963, 1964). In this study, the mortality experience of blood relatives of 270 lung cancer patients was compared to that of an equal number of neighborhood controls matched by race, sex, age, and usual residence. Multiple contacts were used to help improve the reliability of smoking information not obtained directly from an index subject. Mortality from all causes combined and from all cancers

combined was greater among relatives of the lung cancer cases than among relatives of the controls. This excess was primarily in the brothers and mothers of the cases. Respiratory system cancers were significantly in excess among relatives of the lung cancer cases compared to controls; no other organ system demonstrated this difference. Threefold excess mortality from lung cancer was noted in the cases' relatives, and was more marked among males than females. This aggregation of familial lung cancer among relatives of lung cancer patients could not be accounted for by the effects of any of the variables not used for matching. It is unlikely to be due to similar occupational exposures, since the effect was also noted among females. Furthermore, air pollution or common environmental exposures are an unlikely explanation since controls were matched to cases by residence. These results might even be extended to non-malignant respiratory disease mortality, as an indicator of possible genetic predisposition to a variety of respiratory ailments, since case relatives demonstrated excess non-cancer respiratory diseases, as well. Because the blood relatives of cases tended to smoke, whereas the relatives of the controls did not, this study would also suggest that genetic factors have a role, not only in lung cancer etiology, but also

in a concomitant predisposition to smoking which would result in an overestimation of the lung cancer risk associated with smoking. The alternative explanation that, regardless of genetic predisposition, children of parents who smoke also would tend to smoke does not account for the fourfold excess among non-smoking relatives of cases.

Ooi, et al (1986), using relatives of spouses as a comparison group for relatives of lung cancer cases, also found excess risk of lung cancer among relatives of the cases. Cases were selected from death records in ten Louisiana parishes, and telephone or mail interviews were conducted to obtain information on tobacco usage, occupational exposures, and other factors. The study population thus comprised 336 cases (probands), 307 controls (spouses) and their families. Relatives of probands and controls did not differ appreciably with regard to smoking status, type of tobacco used, or duration of smoking. There were, however, significantly more proband relatives who smoked more than two packs-per-day and who smoked sixty or more pack/years. Regardless of their smoking status, relatives of probands had elevated lung cancer relative risks compared to

relatives of spouses. These risks were statistically significantly elevated for both sexes among smoking relatives, and for females among non-smoking relatives. The greatest risk (RR=4.6) was found among the probands' female relatives who never smoked, in agreement with the magnitude of the effect found in Tokuhata's study. Logistic regression analysis was used to control for the effect of other factors, and the familial factor remained a significant determinant of risk even when smoking and these other factors were eliminated. The study had no obvious major methodological faults, and the likelihood of response bias was minimized by reliability checks, although lung cancer cases' surviving spouses and relatives might intentionally or unintentionally distort the probands' or their own smoking history in some non-random manner. It is also possible that differential responses might have occurred due to the probands' information always being obtained from surrogate respondents, while spouses' information was, usually obtained directly. Furthermore, a larger proportion of the spouses' relatives were alive than were probands', and this might have resulted in differential accuracy of the information obtained. The authors suggest that their findings "may be interpreted to support the

presence of a susceptibility gene to lung cancer." However, the finding of increased prevalence of other cancers among probands' families appears to indicate increased susceptibility to several types of cancers. A report from the same study on the risk of non-lung cancer among relatives of lung cancer patients demonstrates greater risk for these cancers among more members of the proband's families (Sellers 1987). Nevertheless, the bulk of the excess cancers among probands' relatives was for sites usually associated with smoking, i.e. lung, nasal cavity, larynx, and cervix.

The mechanisms for development of some neoplastic disease are thought at the molecular level to be related to the activation of certain genes (proto-oncogenes) into "oncogenes" with structural abnormalities that make them contribute to the process of malignant transformation (Rodenhuis 1987). The oncogenes that appear to have a role in human lung cancer are members of the families of genes called myc and ras. Rodenhuis, et al (1987) studied the prevalence of mutational activity of ras oncogenes in tumor specimens of untreated non-small-cell lung cancer. They detected mutational activity of the K-ras gene in five of 35 specimens; all 5 were adenocarcinomas. The

five patients from which these specimens were taken were heavy smokers, whereas two of the patients with a K-ras-negative adenocarcinoma had never smoked. Although this series is small, it does point out differences at the molecular level, reflected in differential ability for K-ras mutational activity, that also are related to cigarette smoking status.

Samet, et al (1986) compared familial and personal respiratory disease histories of lung cancer cases ascertained by a state-wide tumor registry, and matched control subjects selected randomly from lists of telephone numbers and Medicare participants. Subjects or their surrogates were interviewed about tobacco use, residential and occupational history, diet, occupation, and disease history. An analysis of the 518 cases and the 769 controls demonstrated significantly higher prevalence of lung cancer and "other unspecified cancers" in parents of the cases compared with parents of the controls. No difference in prevalence was noted for cancers in grandparents of the two groups. Multiple logistic regression analysis revealed a significantly elevated odds ratio (5.31, CI=2.21-12.76) for parental history of lung cancer. This type of analysis

adjusted for cigarette smoking by the subjects, and thus should not reflect concordance of smoking habits between parents and children. The study used self-reports for control subjects and both self and surrogate-reported information which could not be checked for reliability. Given that the study contrasted diseased cases with healthy controls, it is possible that information bias due either to the different types of respondents or to their different health status might partially account for the observed results.

A recent brief report from a similar epidemiologic study confirms these findings. Kramer, et al (1987) compared lung cancer incidence over a twenty-five year period among first-degree relatives of lung cancer patients and among controls. A significantly increased twofold risk was found for relatives of the cases. The relative risk was higher among non-smoking relatives, and highest among non-smoking relatives of smoking cases. The authors suggest that these results indicate a lung cancer aggregation in families which is only partially due to a familial tendency to smoke.

Among the host factors studied for their influence on susceptibility to lung cancer are the genes controlling the enzymatic oxidative metabolism of chemicals (procarcinogens) by enhancement of metabolic activation, or by inactivation of activated metabolites. Clearly, the actions of these enzyme systems relate to genetic predisposition to cell types associated with smoking (i.e. squamous cell and small cell carcinomas), although Yoneyama, et al (1986) have demonstrated a potential genetic basis for adenocarcinoma of the lung among non-smokers. One enzyme system, the aryl hydrocarbon hydroxylases (AHH), has been studied extensively, in part because its induction is controlled by a single gene locus in mice. However, in man several AHH enzymes exist, each controlled by a different gene, and results relating AHH activity or AHH inducibility to lung cancer in humans have been inconsistent (McLemore 1981, Rudiger 1985). Rather than the activity of individual enzymes, Rudiger, Nowak and others compared the amount of relevant activated metabolites, determined as DNA adducts, in monocytes of lung cancer patients and healthy controls (Rudiger, et al 1985, Nowak 1987). They found, in concordance with results from in-vivo and epidemiologic studies on metabolic oxidation of debrisoquine (a

non-toxic test compound) (Ayesh 1984, Idle 1983), that patients considered to be cancer-prone showed approximately twice as much of activated metabolites as the controls. As expected, no differences were found between smokers and non-smokers. It seems possible that the increased adduct concentrations were due to the disease, rather than being a cause of the disease. The authors, citing only a slight elevation in adduct levels in patients with a family history of cancer, argue, somewhat unconvincingly, against this. Seidegard, et al (1986) studied the occurrence of the comparative distributions of the activity of glutathione transferase (towards trans-stilbene oxide as substrate, GTtSBO), a Phase II enzyme controlling the detoxication of reactive intermediates of oxidative metabolism, among lung cancer patients and controls. They found a greater proportion (59.0%) of the controls who smoked had GTtSBO than did lung cancer patients who smoked (34.8%). This difference was statistically significant among heavy smokers. Thus, these data suggest a biological mechanism for increased susceptibility of some individuals to smoking-induced lung cancer, since many potentially carcinogenic components of cigarette smoke are known to be conjugated by glutathione transferase.

Substantial evidence exists to support the conclusion that lung cancer is largely a genetic disease (Hansen 1987). Although the magnitude of the genetic component of lung cancer etiology probably is in the order of a 10-100 times higher incidence among susceptibles, this effect "can be surprisingly difficult to detect"....but "may account for a substantial proportion" of lung cancers (Peto 1980). Recently, it has been reported that a genetic defect in chromosome 3 contributes to the development of small cell lung cancer, a type of the disease which accounts for 30,000 to 40,000 cases annually. The involvement of chromosome 7 in non-small cell lung cancer has been suggested by Lee, et al (1987). Other data suggest that there are financial factors in serum selenium and Vitamin E levels of lung cancer patients (Miyamoto 1987) which may reflect on interaction between a genetic and a dietary etiological components.

DIETARY INFLUENCES

Several retrospective and prospective epidemiologic studies have consistently shown a relationship between certain dietary components and reduced risk of lung cancer (Colditz 1987, Byers 1987, Wu 1988, Koo 1988). Within the last few years, additional studies have confirmed these observations, refined the association with specific components of the diet, and demonstrated how smoking-related risk might be misinterpreted because population studies have not accounted for dietary differences.

The importance of dietary factors, including cooking practices, in the etiology of lung cancer is underscored by recent results from a case-control study among women in China (where few women smoke cigarettes) (Gao 1987). This study found an association between lung cancer and exposure to cooking oil vapors, prompting the authors to suggest that factors other than smoking are responsible for the high lung cancer risk in Chinese women.

In the NHANES I Epidemiologic Follow-up Study, a cohort study based on the National Health and Nutrition Examination Survey conducted from 1971-1975 on a probability sample of the non-institutionalized U.S. population, Shatzkin, et al (1987a) calculated cancer incidence and mortality rates among persons with different serum cholesterol levels. Data on age, education, smoking, alcohol consumption, etc. were collected by personal interview, and cholesterol level was determined from collected blood samples. Median follow-up time from the initial interview was 10 years for the 5,125 males and 7,363 females in the incidence analyses and for the 5,791 males and 8,535 females in the mortality portion. The results demonstrated an inverse association between cholesterol level (by quintile) and leukemia, lung cancer, bladder cancer, and pancreatic cancer in both sexes, and cervical cancer in women. Cancer risk among men in the lowest quintile was almost double that of men in the highest quintile for both incidence and mortality. Among women, the mortality risk was the same as among males, but the incidence in the lowest quintile was only 1.2 times higher than the highest quintile. These results are unlikely to reflect a "preclinical cancer effect", i.e. decreased total serum cholesterol as a result of

cancer, since the inverse relationship was strongest for cancers diagnosed 6 years or more after cholesterol was measured, and did not diminish with increasing time between determination of cholesterol and diagnosis of cancer. Because the inverse relationship was especially prominent for the so-called "smoking-related" cancers, with a relative risk of 2.0 (1.3-3.0) for the lowest compared to highest quintile (Shatzkin 1987b), the likelihood of a biased association with smoking is evident.

This inverse association must be considered along with data from Wynder, et al (1987) which show a highly statistically significant international correlation between the proportion of calories from dietary fat and lung cancer mortality. This analysis accounted for smoking by including tobacco disappearance data from each of the 43 countries in the study. Several potential biological mechanisms exist for the initiation or promotion of lung cancer by a high-fat diet, and the literature is replete with experimental evidence of its carcinogenicity. The apparent anomaly with the findings of Shatzkin, et al (1987) probably reflects the importance of genetic and other factors in addition to cholesterol intake in determining serum

cholesterol level. In any event, these two studies demonstrate the potential effects of cholesterol level and fat intake on lung cancer risk, although other dietary factors are important, as well.

In a carefully conducted recent study (Byers 1987), a modified food frequency method was used to obtain information on usual diet (prior to one year before onset of symptoms) from 450 incident lung cancer cases, and from 902 general population control subjects. The need for gathering information on other potential risk factors resulted in a rather long interview which could only be administered to patients tolerant subjects. Consistent with previous studies of the same design, this investigation found an inverse relationship between intake of vitamin A from fruits and vegetables (carotene) and lung cancer risk. The association was strongest (i.e. the risk was reduced most; about 50-80%) for squamous cell carcinoma, in concordance with previous results (Kvale 1983, Byers 1984, Zeigler 1984), and also for older males, male ex-smokers, and for male current smokers with less cumulative lifetime cigarette exposure. Neither vitamin E nor vitamin A from animal sources (retinol) resulted in a risk reduction. It is possible, because of the selection criteria for this

study, that bias was introduced by excluding the most ill cases or those who died before they could be interviewed. Dietary recall may have been different between cases and controls due to knowledge of their disease status or to the slightly different time periods involved. Furthermore, less than half of the eligible controls completed their interview, and if their non-participation were related to dietary practices, this could represent an additional source of bias.

Zeigler, et al (1986), in the largest study of diet and lung cancer to-date found very similar results. Their population-based case-control study among men in New Jersey included 763 cases and 900 controls who has been interviewed approximately four years earlier about their usual frequency of consumption of 44 food items. In concordance with Byers, et al (1984), they found no association between lung cancer and intake of retinol or total vitamin A, but did find a 30% (non-significant) excess risk associated with low or medium intake of carotene. A statistically significant trend in reduced risk associated with increasing carotene intake was found among current smokers and ex-smokers of one year or less. They also found that the reduced risk was most apparent for squamous

cell carcinomas, although it extended to other cell types when only current and recent smokers were analyzed. In addition, the study found that intake of dark green leafy vegetables offered a greater protective effect than did intake of retinol. The highest consumption of vegetables was found among non-smokers, and tended to decrease with increasing duration of smoking. Intensity of smoking was not related to consumption of vegetables. While the influence of vegetable intake on the risk of lung cancer is not very strong, (RR=1.38 for lowest vs highest consumption after adjusting for smoking), the large percentage of the population with low consumption results in a lung cancer population-attributable risk of 22%. One possible source of bias in this study is the use of licensed drivers as controls. These people probably represent a different population from the case source, and may have introduced some non-comparability in dietary habits, recall, or unmeasured potentially confounding factors.

Pastorino, et al (1987) compared the serum levels and dietary intakes of retinol and carotene of 47 females with histologically confirmed lung cancer with those of 159 hospital controls. Blood samples taken the day after admission and dietary history questionnaires

administered by dieticians were used for the determination of vitamin A intake and serum level. Odds ratios calculated by comparing tertiles of retinol and beta-carotene in serum and diet (controlling for cholesterol, triglycerides, etc.) were elevated for the lowest vs the highest blood and intake levels. The ORs for plasma carotene were statistically significant for the combined low and medium tertiles compared to the highest, as was the trend. Though not significant, there was a trend of increasing risk with decreasing serum and dietary retinol and with dietary carotene. Interestingly, the authors noted that in this study, women who smoked for less than 25 years or who smoked less than 20 cigarettes per day, had half the lung cancer risk of non-smokers.

The protective effect of vitamin A on lung cancer risk also was observed in a population quite different from those discussed above. Kolonel, et al (1985) conducted a lung cancer case-control study in Hawaii, using tumor registry-identified cases and age- and sex-matched controls selected by random digit dialing. Spouses served as surrogate respondents for 24% of the cases. Based on interview data collected on 364 patients and 627 controls, an odds ratio in males of

1.8 (1.1-3.1) was calculated for the lowest vs the highest intake group, with a clear dose-response effect based on weekly total vitamin A intake. No effect of vitamin A was found in females. Analyses based on vitamin A food sources only, or on retinol sources only yielded similar results. Though no data were presented, the authors noted that results among cigarette smokers were similar to those found in the male subjects.

In a study examining the role of vitamin A as a risk factor for cancer of any site, Middleton, et al (1986) confirmed previous observations made on lung cancer patients only. The relative risk was 34% lower among males with the highest intake level vs the those with lowest level. After adjustment for smoking the risk was 27% lower. A statistically significant dose-response relationship also was noted. In females, a slight, non-significant risk reduction was seen. Interestingly, in males vitamin A showed a protective effect specifically for several sites which have been associated with smoking. This may account for the apparent sex-specific effect on these squamous cell tumors, given the different smoking habits of males and females. With so many sites included in this study, it is

possible that some statistically significant associations actually were due to chance. In addition, because information was collected on dietary habits one year prior to symptoms onset, the relevance of these data for etiological aspects is questionable since lung cancer generally has a rather longer latency period.

The apparent inverse association between vitamin A intake or serum level and lung cancer risk is particularly important in the context of our extended appraisal because it demonstrates a reasonable pathway which leads to the spurious indictment of smoking. Cross-sectional studies have shown lower plasma levels of beta-carotene in smokers compared to non-smokers (Stryker 1988, Aoki 1987). In turn, this has led to suggestions that one way in which smoking might affect lung cancer risk is by reducing the level of protection associated with higher intakes of vitamin A. However, closer examination of the aforementioned reports reveals that alcohol consumption has a much larger effect on lowering serum vitamin A levels than does smoking. Thus, the apparent association of smoking with lowered vitamin A levels probably reflects, to a great degree, the strong correlation between alcohol and tobacco usage. Furthermore,

it may reflect a particular lifestyle which includes lower intake of leafy green vegetables and other sources of dietary vitamin A, which in turn comprises certain activities, propensities, or genetic predispositions which might be independently associated with increased risk of lung cancer. A recent comparison of the dietary habits of smokers and non-smokers in Great Britain exemplifies these differences (Whichelow 1988). In this study, approximately 9,000 randomly-chosen adults were interviewed about their dietary, smoking, alcohol and exercise habits. The investigators found definitive differences between smokers and non-smokers in eating behaviors which manifested themselves in a pattern of a typically unhealthy diet. Of particular pertinence are the findings that the diets of ex-smokers was similar to that of never-smokers, and that the diets of heavy smokers differed more from that of non-smokers than did the diets of light-smokers.

Based on estimates advertised by the U.S. Environmental Protection Agency (EPA), a substantial portion of lung cancer incidence in this country is due to exposure to radon in the domestic environment. These estimates are rather controversial, and exemplify the non-scientific factors which affect government-promulgated estimates of the risks to health from a variety of sources. For example, a recent Science article trumpets in its headline, "The radon seeping into homes may be killing 5,000 to 20,000 Americans per year; the best action may be to stop smoking" (Kerr 1988). As incongruous as this sounds, it becomes ludicrous when one reads the articles and notes that this mitigating strategy derives from a National Research Council committee which "assumed that radon risk multiplies the existing risk of dying of lung cancer...". The article continues, noting "In fact, the data did not best fit such a purely multiplicative model." The EPA has estimated that 5,000 to 20,000 lung cancer deaths each year are caused by radon (US EPA 1987). Following a 10-state survey of radon levels, the EPA revised its estimates of the number of homes with potentially dangerous levels upward by about

a factor of two. Yet, the estimated number of attributable cancer deaths remained the same (perhaps because upward revision would have accounted for 31% of all lung cancer deaths). Apart from the internal economies of the EPA which drive their estimation procedures, the problems with estimation of lung cancer population-attributable-risk due to exposure to radon in the home also derive from several scientific considerations: 1) The estimates are based on extrapolation from epidemiologic studies of uranium miners; 2) No representative sampling of radon levels in U.S. homes which takes account of seasonal, diurnal, and intra- and inter-house variation has been completed; 3) The distribution of homes with high radon levels is not uniform across the U.S., and attribution of 20% of lung cancers to exposure to radon thus implies a substantially higher proportion in some areas of the country; and 4) Only recently has any study of lung cancer due to residential radon exposure, which would allow the extrapolations to be verified, been published. It is worthwhile to expand on these considerations to appreciate fully the nature of the radon/lung cancer association.

Firstly, radon daughter dosimetry is very difficult because it involves a combination of factors such as respiration rates, particle size distribution, lung deposition, and Rn/Rn daughter equilibrium (Hornung 1987). Secondly, the miners' exposures were derived not only from actual measurements, but more often by extrapolation over time, estimation by geographic area, and estimates of early (before 1950) exposure based on knowledge of ore bodies, ventilation practices, and earlier measurements (Lundin 1971, Sevc 1988). Actual measurements were available only about 10% of the time, and the overall error in exposure measurement has been estimated at 137% (coefficient of variation) or about a 97% relative standard deviation of the total (working level month) for each miner (Hornung 1987). The extrapolation of risk derived from the miner studies to estimate risks due to exposure in the home introduces additional problems. In contrast to the population most highly exposed in the home, miners comprised males performing heavy manual labor in a very dusty environment. Risk estimates derived from this population, therefore, could be expected to overestimate the risk due to domestic exposure, even if the radon levels in the home were the same as in the mines.

Although a systematic appraisal of radon levels in U.S. homes has never been conducted, some estimates of these concentrations do exist. Nero, et al (1986) estimated the distribution of radon levels in U.S. homes from data on 38 areas, none of which were selected using statistically-based sampling procedures. These measurements typically were made in homes of volunteers, with expectedly higher levels, and by a variety of methods with differential validity and reliability. Arithmetic mean Rn222 levels ranged from 2.57 picocuries per liter (1377 homes) to 1.42 for those sites not having a prior expectation of high concentrations (817 homes). According to Nero, et al, these levels translate into a lifetime lung cancer risk of 0.3% (the EPA estimates it as 1.0%), or about 10,000 cases of lung cancer annually.

The study by Svensson, et al (1987) represents the first epidemiologic evidence of a relationship between exposure to radon at levels commonly encountered in the home and bronchial cancer. 292 female lung cancer cases identified from a local cancer registry, and 584 population controls constituted the study population. The cases

were restricted to women with cancers of the "unspecified epithelial group." Homes in which cases or controls had lived for at least two years were dichotomized by geological criteria and by whether the subject had lived close to the ground floor, into categories of "radon risk" or "no radon risk." All radon-positive homes and some of the negative homes (about 10% of the total number of addresses) were measured for radon level by a grab-sample technique. Data on the subjects' smoking habits were not obtained, although information from a national survey in 1963 was used as an estimate. Statistical analyses revealed a relative risk of 2.2 (1.2-4.0) for exposure to radon, or 4.1% of the cases attributable to that exposure. However, when actual measurements were used, the differences in radon/radon daughter concentrations between residences of cases and residences of controls were not statistically significant. The available smoking data indicated that smoking among women was not more common in the areas where higher radon levels were estimated, so the possibility of confounding is lessened somewhat. However, it is known that the presence of a smoker in a residence can affect radon levels, and this information is lacking in this study. It is not even clear just how smoking affects radon dose; some believe passive smoking increases

lung dose by increasing the equilibrium ratio of radon daughters (Winters 1983), while other evidence points to lower levels of total body contamination in smokers (Stebbings 1986). Evidence from experimental studies in dogs shows that cigarette smoke plays a protective role in suppressing radon-daughter-induced lung consequences (Gies 1988). In fact, depending on how smoking is factored into a radon risk assessment, the process introduces a range of risks over an order of magnitude (Ginevan 1986).

Since it is the polonium decay products of radon (Po-218 and Po-214), that deposit on the bronchial airways and deliver the carcinogenic dose (Harley 1986), it has even been suggested (Ravenholt 1987) that tobacco smoke containing polonium (Po-210) is a major source of the alpha particle activity attributed to radon. However, Letourneau, et al (1987) have shown that, in fact, the alpha particle activity inside a house is by four orders of magnitude predominantly due to radon and its short-lived progeny.

In the Svensson, et al study, the absence of actual radon daughter measurements on all residences is a most serious shortcoming, and

the grab-sample technique used for the study, is unreliable because levels vary from house-to-house and over short periods of time. It is generally accepted that the magnitude of radon levels in homes, which depends on house-to-soil coupling, soil moisture, indoor-outdoor pressure differences, air-exchange rate, etc. cannot be predicted very well either by geological criteria or proximity to homes with known radon levels.

Nevertheless, Stockwell, et at (1988) conducted a case-control study to determine if residence in an area with high natural radioactivity (i.e. with a large percentage of homes built on land reclaimed after mining of phosphate deposits containing uranium and members of its decay series) is associated with increased lung cancer risk. Actual levels of radon in homes were not measured. Male nonsmoking residents of the area were at elevated risk for all lung cancer, and specifically for adenocarcinoma, squamous cell carcinoma, and small cell carcinoma compared to residents of other parts of Florida. No statistically significant excess risks were found for male smokers or for females. The study suffers from not having actual measurements or radon levels lung cancer cell types was attempted.

OCCUPATION

Increased risk of lung cancer is associated with employment in a variety of industries. Among the jobs known to be at elevated risk are pesticide production, coke oven operation, roofing, mining, chemical industry, smelting, beryllium production, metal industry, shipyards, and dry cleaning. Recently, Simonato, et al (1988) attempted a systematic evaluation of the proportion of lung cancers due to occupational exposure by calculating population attributable risks from data in published studies. The authors' estimates were in the same general as commonly accepted, centering around 15%. They concluded that for selected populations residing in specific areas, the proportion of lung cancers attributable to occupation could be as high as 40%. A few recent studies suffice to exemplify the risk due to occupation, and the wide range of jobs associated with increased risk. Ronco, et al (1988) examined lung cancer and occupation in two industrialized areas of Northern Italy. Attributable risk percentages for occupation in the two areas were about 36% and 12%. Among the job categories showing excess risk were structural mental work, welding, electrical machine production, woodworking, and cleaning services. Carstensen, et al (1988) found excess lung cancer risk

among a cohort of Swedish bakers and pastry cooks. Wicklung, et al (1988) found an excess among orchardists in Washington State. They had hypothesized that any excess would be due to lead arsenate exposure, but a comparison of lung cancer cases and controls found no difference in presence, intensity, or duration of such exposure. The excess risk could not be attributed to cigarette smoking, and its cause remains unknown. A retrospective cohort study of marine engineers and machinists in Iceland found statistically significantly elevated lung cancer mortality risk to these occupations (Rafnsson 1988). Enterline, et al (1988) updated an earlier study of mineral fiber workers, and confirmed their excess respiratory cancer risk. The excess risk appeared to be specific for mineral wool workers but not for fibrous glass workers. Exposure to mineral oils from employment in a Norwegian plant which manufactured high voltage wires was found by Ronneberg, et al (1988) to increase the risk of lung cancer. Oil impregnated paper insulation for the cables was the source of the exposure. Pipefitters and platers in Finnish shipyards had excess risk of lung cancer incidence compared to regional urban rates (Tola 1988). In France, excess risk of lung cancer was found to be associated with employment as farmers, miners and quarrymen,

plumbers and pipefitters, and motor vehicle drivers (Benhamou 1988).

The variety of occupations in which the risk of lung cancer is elevated is clear. In addition to limiting the possible contribution of smoking to lung cancer causation, the occupational factor provides a pathway for smoking to be wrongfully implicated as a cause. This could occur if persons employed in occupations with higher risk of lung cancer happen to smoke more than persons employed in lower-risk jobs. Confounding of sort would not be unexpected since both occupation and smoking behavior are related to social class, as shown in a recent (Brackbill 1988) analysis of data from the National Health Interview Survey. Stellman, et al (1988) investigated this phenomenon in a population enrolled in the American Cancer Society's large prospective survey. They found that smoking rates were significantly higher in groups exposed to a variety of occupational hazards than in non-exposed groups. The differences were most notable for men, particularly for those exposed to asbestos, coal or stone dust, dyes, textile fibers, and chemicals or coal tar pitch.

CONCLUSIONS

The number of cancer deaths in the United States attributable to smoking is not as clear-cut as generally assumed. Based on rates from the National Cancer Institute's SEER program, the American Cancer Society estimates that 130,100 lung cancer deaths occurred in 1986 (American Cancer Society 1986). The estimated number of cases in 1986 was 149,000. The EPA estimates for the number of lung cancer deaths due to radon exposure are undoubtedly high at 20,000 (15.4%), and may be more realistic at 4% or 5,200. If, as suggested in the literature, occupational exposures account for another 15% (19,500), and diet for 20% (26,000), it is unlikely that smoking could be responsible for even half of the U.S. lung cancer deaths. This does not consider the effects of urbanization, stress, and air pollution. Furthermore, it neglects the evidence for a detection bias in the diagnosis of lung cancer, in which non-smokers are less likely to have _____ cytology performed (Wells 1988) and lung cancer is 37 times more likely to be correctly diagnosed in smokers than in non-smokers (McFarlane 1986a,b). Of course, this bias would result in falsely high estimates of the actual magnitude of the

smoking/lung cancer association. It does not take into account the familial host-susceptibility factor evident from genetic epidemiologic studies which "must have a substantial influence on lung cancer mortality" (Lynch 1981). Nor does it account for the effect of mineral particle deposition (Chung 1988). Finally, it fails to consider the potential effects of climatic and ecologic conditions, as demonstrated by Weinberg, et al (1987).

Therefore, "risk factor" most lay people assume to predominantly "cause" lung cancer may not even be the major "cause" of the disease. Support for this argument derives from descriptive epidemiologic evidence about the distribution of the disease and it's component cell types in time and among different population groups, and from a substantial amount of scientific literature detailing other major risk factors. Clearly genetic predisposition to lung cancer and to neoplastic diseases of other sites contributes greatly to the etiology of these diseases. Dietary habits and occupational exposures are well-documented as risk factors, and radon exposure has lately been taking on increased significance. Since these risk factors are comparatively difficult to measure, and usually have not been

adequately, if at all, taken into account in the case-control studies of smoking which have formed the basis for smoking risk estimates, these estimates must be erroneous. Certainly, there are other factors such as detection bias which contribute to lung cancer incidence and to a spurious implication of smoking. While information about risk factors other than smoking permeates the scientific literature, the public seemingly is unaware of its existence. This literature is recent, funded from a variety of sources, and has been reviewed herein with if anything, a bias toward conservatism, (witness the downgrading of the EPA estimates of the number of lung cancer cases attributable to radon). Thus in the end, when one considers the global picture, the commonly attributed role of cigarette smoking as a possible risk factor for lung cancer must be an overestimate.

Although there exists some perception of an etiological role for smoking in asthma, scientific evidence strongly disputes this. A national survey of asthma prevalence in the U.S. found asthmatics to be current smokers as frequently as non-asthmatics (Gergen 1988). In the published report of this survey, the authors noted similar observations reported from Australia and England.

In addition, two New Zealand studies, one on national asthma mortality and the other a regional case-control investigation, found young age, non-Caucasian race, and poor medical care to be associated with an increased risk of death among persons with asthma. (Sears 1987; Morse 1987a,b) Neither age at onset of asthma, family history of asthma, nor smoking habits were associated with increased mortality risk. In Papua New Guinea, a 15-year prospective follow-up study of mortality from chronic lung disease found no association whatever between smoking and severe respiratory symptoms or reduced lung function (Anderson 1988).

Non-specific bronchial hyper-responsiveness (BHR) is regarded as critical to the development of symptoms in asthmatics. It may also occur transiently after a respiratory infection or exposure to ozone, or

chronically due to immunologic sensitivity to substances such as western red cedar (Vedal 1988). The tree main theories for the origin of BHR are allergy, inflammation, and altered geometry. Pride (1987, 1988) found slight abnormalities in eosinophil count and IgE levels in smokers, but could not relate these to the presence of BHR. He found nothing to confirm an association between chronic inflammation of bronchial walls in smokers and BHR. Suzuki, et al (1988) found that the smoking of a single cigarette by healthy non-smokers did not change their bronchial responsiveness.

Since 1963, it has been known that decreased protease inhibition is associated with the pathogenesis of emphysema. This protease inhibition is due to a homozygous genetic deficiency of alpha-1-antiprotease (AAP) which allows enzymatic action on lung elastin. (Idell 1987) Recently, Satoh, et al (1988) have identified a single base substitution causing AAP deficiency in addition to previously identified homozygotic mutations causing identical respiratory consequences. The symptoms of emphysema associated with AAP deficiency begin before the age of 40 in most cases, and before the age of 50 in almost all. However, while individuals with certain inherited combinations of the alpha-1-antiprotease gene invariably develop emphysema, not all AAP-deficient individuals eventually develop the disease. In contrast to the obvious explanation in genetics, it has

been suggested that an effect of cigarette smoking is to increase the load of protease which must be inactivated and decrease the level of AAP. However, this hypothesis does not explain why emphysema does not develop in all cigarette smokers. According to Resendes (1987), "Although many explanations have been offered, this question remains unanswered."

There is evidence in the scientific literature that smoking-induced processes protect the lung against certain environmental hazards. This hypothesis was suggested some 30 years ago as an explanation of the observation that coal miners with bronchitis appeared to develop less pneumoconiosis than miners without the bronchitis. Sterling (1983) has hypothesized that one result of smoking is production of a layer of mucus which, by lining the respiratory tract, blocks the access of a potential carcinogen to the mucus membrane, or dilutes and clears these substances more effectively than normal. Albert, et al (1975) studied short-term bronchial clearance in nine non-smokers and six smokers. By comparing the clearance times of two radioactively-tagged aerosols, the second followed soon by the smoking of two to seven cigarettes, they found that in both smokers and non-smokers cigarette smoking resulted in a least a twofold speed-up in deep bronchial clearance. They postulated that an

increased mucus production was related to the observed effect on particle clearance.

Other investigators have found a qualitative difference in the composition of bronchial mucus between smokers and non-smokers. (Kollerstrom 1977) The acid mucins synthesized by the cells of the bronchial glands have either sialic (neuraminic acid) groups or sulphate groups on their side chains. The ratio of the amount of sulphated to sialic acid mucin was greater in smokers that in non-smokers, and clearly distinguished the two groups. The practical significance of this difference, however, is not clear.

Whether the mechanism is, in fact, related to increased clearance ability or to some immunologic response, smoking also appears to offer protection from other respiratory diseases. Extrinsic allergic alveolitis is one cause of pulmonary alveolar fibrosis, and is a result of an excess immune response to inhaled antigens. Warren, et al (1975), noted in their studies of lung mechanics of patients with extrinsic allergic alveolitis that most were non-smokers. Subsequently, Warren (1977) compared smoking histories of patients diagnosed with this disease with histories of patients with cryptogenic alveolitis or sarcoidosis and also with information obtained from a random sample of the local Manitoba population and

a group of 100 farmers entering the hospital with any diagnosis. Smoking habits among men with extrinsic allergic alveolitis differed significantly from those of the other two disease categories combined. The proportion of non-smokers in the allergic alveolitis group was significantly greater than in the local population or the group of farmers. All females with allergic alveolitis were non-smokers.

ESTROGEN DEPENDENT CANCERS

SMOKING AND ESTROGEN SECRETION

Smoking has been shown to have an hormonally mediated effect on reducing the risk of cancers of the breast and endometrium. MacMahon, et al (1982) demonstrated a reduced excretion of endogenous estrogens in urine samples from women who smoked; Greenberg, et al (1987) found that hormonal replacement therapy users were more likely to smoke than were non-users; Jick, et al (1977) showed that smokers experienced menopause at an earlier age. Interestingly, Hartz, et al (1987) recently found that smoking was associated not only with early natural menopause (age-adjusted OR=1.6) but also with surgically induced menopause (OR=1.5).

Prior to menopause, the ovaries are the source of estrone and estradiol, while after menopause, the principal source of endogenous estrogens is through conversion of androstenedione, produced by the adrenals. Fat mass, a known endometrial cancer risk factor, is a major determinant of this conversion to estrone. Jensen, et al (1985)

examined 136 post-menopausal women treated with exogenous estrogens to determine the effect of smoking on serum levels of estrone and estradiol. They found reduced levels of both hormones in smokers, particularly among women taking higher doses of exogenous estrogens. There was a statistically significant inverse dose-response relationship between amount smoked and serum estrogen level, with smoking having no effect among women not taking exogenous estrogens. The authors suggest that the lower estrogen levels in smokers result from increased metabolism of estrogens in the liver, rather than lower estrogen production as suggested by MacMahon, et al (1982) in their study of pre-menopausal women.

Michnovicz, et al (1986) demonstrated that smoking leads to decreased bioavailability of the estradiol metabolites which possess potent estrogenicity. Daniell (1987) contends that if this were the case, administration of exogenous estrogens would override this deficit. Thus, estrogen antagonists, which may either be absorbed during tobacco usage or produced in the body during smoking, substantially contribute to the observed anti-estrogenic effect of

smoking. Michnovicz and Fishman (1987) agree with the possibility of a role for estrogen antagonists as one of several multiple mechanisms.

Friedman, et al (1987) confirmed the absence of a smoking effect on estrogen level among post-menopausal women not under estrogen therapy, but did note a significant elevation of progesterone among smokers. They suggest that it is this increased progesterone level which partially protects smokers against endometrial cancer. Recent results from Khaw et al (1988) support this suggestion that the protective effect of smoking may be mediated by increased androgenic activity instead of reduced estrogenic activity.

ENDOMETRIAL CANCER

Each year, approximately 40,000 women in the United States are newly diagnosed with cancer of the endometrium, and about 3,000 women die from this disease (Tyler 1985). Known risk factors including obesity, certain medical conditions, reproductive factors, and socioeconomic status have been well-documented for over 10 years (Elwood 1977, Kelsey 1982), but evidence demonstrating an apparently protective effect of cigarette smoking has only recently been accumulating. It has been well-documented that smokers weigh less than non-smokers, that smoking cessation results in weight gain, and that this gain is relatively permanent for at least 25 years after cessation. (Blitzer 1977) Thus, smoking probably exerts it's protective effect both by weight control and by anti-estrogenic activity.

In a multi-center case-control study, Lesko, et al (1986) compared medical and reproductive histories, and data on drug, alcohol, and cigarette usage from 510 invasive endometrial cancer cases, ages 30

to 69, with data from 727 control women admitted for selected malignant conditions judged to be unrelated to cigarette use. Excluded from the control series were women who had a hysterectomy or bilateral oophorectomy. The median age of the cases was 59 years compared to 52 years for the controls. Twenty-two percent of the cases were current smokers; 29% of the controls currently smoked. In an analysis which controlled for age, body-mass, and duration of conjugated estrogen use, a rate ratio (RR) of 0.7 (0.5-1.0) for current smokers vs never-smokers was calculated. The RR for smokers of 25 cigarettes or more per day was 0.5 (0.3-0.8), while for those who smoked fewer cigarettes or were ex-smokers, the rate-ratios were not significantly different from unity. One finding of particular interest is that the effect of cigarette smoking on endometrial cancer risk depends on menopausal status. The rate ratio for heavy smokers among post-menopausal women was 0.5, while among pre-menopausal women the RR was 0.9. Exogenous estrogen use had no effect on the risk estimate. Although this study was well-designed and analyzed, the finding of an apparent protective effect of smoking has been dismissed as spurious by several critics. Alternative explanations for this finding include the

age difference between cases and controls (Nordenstam 1986), the possibility of a genetic predisposition both to smoking and to having a lower risk of endometrial cancer (Burch 1986), the use of some controls having colon-rectal cancer (Imrey 1986) or other cancers (Lashner 1986), and the possibility that intentional exclusions, such as of women with hysterectomies, or unintentional exclusions due to premature death from other causes among heavier smokers (Ravenholt 1986). For the most part, none of these criticisms appears to have much basis. Age differences were, in fact, controlled in the statistical analyses. The absence of reduced risk among former smokers argues against a genetic predisposition to both smoking and decreased disease risk. Lesko, et al (1986) noted that the colo-rectal controls had similar smoking histories as the other control patients, and that the neoplastic diseases included in the control series had not been previously associated with smoking. Furthermore, they stated that the proportion of current smokers among the controls was similar to that among women in the general population. Nevertheless, the use of control subjects without tobacco-related diseases probably would tend to decrease the rate ratio for smoking. The argument that smokers might die from a tobacco-related death

before they would enter into a study as a case is faulty because it would also preclude their entering as a control. In any event, the use of cancer patients as controls in the present study helps to ameliorate any potential problem. Premature death related to smoking would have to have occurred at different rates between women destined to have endometrial cancer and those destined to have other (control series) cancers.

Lawrence, et al (1987), using a population-based case-control design, selected from hospital files in upstate New York women ages 40 to 69 diagnosed as having early-stage endometrial cancer. These cases were confirmed histologically. Controls were selected from motor vehicle files, and were matched by county of residence and age to each case. Medical, reproductive, and smoking histories were collected by in-person interviews. Smokers of a pack or less per day had a relative risk of 0.7 compared to non-smokers, while those smoking more than one pack per day had a risk of 0.5. Among former smokers the corresponding relative risks were 1.0 and 0.60. Among both pre- and post-menopausal women, the relative risk for smokers compared to non-smokers was 0.6. Although these reduced

risks are not statistically significant, a real reduction in risk among pre-menopausal women could not be ruled out. There was no significant dose-response trend in risk reduction among ex-smokers. This study was the first to examine the combined effects of smoking and weight on the risk of endometrial cancer. This study found a modification by smoking of the effect of weight on increasing cancer risk. The largest reduction in risk for smoking occurred in the heaviest women, while no effect due to smoking was found in those weighing less than 140 pounds. Among non-smokers, the estimated disease risk increased up to five-fold with increasing body weight, while among smokers, the risk increased only 40%. Furthermore, among post-menopausal women who did not use exogenous estrogens, relative risk significantly increased with increasing weight, reaching 11.6 for those weighing over 180 pounds. The relative risk did not increase with increasing weight among smokers.

Smith, et al (1984) also used a population-based cancer registry to identify endometrial cancer cases and controls. Controls were frequency-matched by age to the cases, and excluded women with

cancer of the reproductive organs. The joint effect of smoking and weight on risk differed between pre- and post-menopausal women. In the pre-menopausal group, the risk to smokers compared to non-smokers was slightly increased among women with lower body size, but was increased less for heavier women. In neither instance was the risk statistically significantly raised. Among post-menopausal women, in contrast, smokers had lowered risk compared to non-smokers, with the effect being most evident among smaller women. Again, the risk reductions were not statistically significant.

In a recent case-control study of female reproductive cancers, Stockwell and Lyman (1987) compared 1,374 endometrial cancer cases identified through a state-wide cancer registry in Florida with 3,921 controls having diagnoses of either colon cancer, rectal cancer, cutaneous melanoma, or endocrine neoplasms (sites not having a recognized association with smoking). Compared to the cases, the control population was older and more likely to be divorced or widowed. Endometrial cancer risk was not significantly decreased for women who smoked less than a pack per day, but showed a significant inverse dose-response relationship for smokers of more

than a pack per day (0.7-0.5). Former smokers' risks were comparable, although the amount they smoked was not taken into account. The reduced risk was exclusive to women age 50 and older, and while the use of 50 as a surrogate for menopausal status might be questioned, the authors indicated a natural bimodal risk distribution centered at that point, and a median age of menopause in the U.S. at age 52. The use of cancer registry data also introduced some problems, notably the complete absence of data on weight, parity, and exogenous hormone use, as well as tobacco usage for some 25% of the subjects. Nevertheless, the findings compare well with other studies which had more or better information on these factors.

Baron, et al (1986) compared cigarette usage among 476 endometrial cancer cases ages 40-89, with that of 2,128 non-malignant disease control subjects admitted to the same hospital as the cases. Excluded from the control series were women diagnosed with respiratory or circulatory system diseases. Smokers with a history of 15 or more pack-years had an odds ratio, adjusted for other potentially confounding factors, of 0.6 (0.4-0.9) compared to non-smokers, and a

significant inverse dose-response relationship. It is unlikely that this finding was due to differential exogenous estrogen use between smokers and non-smokers since the data were collected between 1957 and 1965, before estrogen use increased in the late 1960's. Smoking rates among women ages 40-89 were lower than those among women born more recently, and the highest exposure category, 15 pack/years or more, represents a comparatively modest exposure. Furthermore, since current smoking status was not assessed, and other studies have shown lower risk for current rather than former smokers, this study would tend to underestimate the effect of recent smoking only.

Franks, et al (1987) used histologically confirmed cases of endometrial cancer between the ages of 20 and 55, and controls selected by random digit dialing in the same geographic areas as the cases. Analyses were based on information obtained from post-menopausal women over age 40 (106 cases, 528 controls). Cases were more likely than controls to be older, obese and to have never used oral contraceptives. The relative risk for endometrial cancer for women who continued to smoke after menopause was 0.5 (0.3-0.8) compared to non-smokers, in agreement with the findings of

Lawrence, et al (1987) The effect was similar among users and non-users of exogenous estrogens. Post-menopausal non-smokers who did not use estrogen replacement therapy had significantly excess risk, 3.8 (1.7-8.2), compared to smokers. Thus, the risk of endometrial cancer among post-menopausal women between 40 and 55 years of age is the same for users of both exogenous estrogens and cigarettes as it is for non-users of both. Though excluded from this study, post-menopausal women who quit smoking before menopause had reduced risk intermediate between, but not significantly different from the non-smokers and post-menopausal smokers. These results confirm the earlier findings of Weiss, et al (1980) of a reduction due to cigarette smoking in the increased risk from exogenous estrogen use. While the excess risk from estrogen therapy was not totally nullified by smoking in this earlier study, the reduction was greater for longer duration of estrogen use, amounting to an almost five-fold reduction among those women using estrogen for eight or more years.

The apparent protective effect of smoking on the risk of endometrial cancer received further confirmation in a recent study conducted in

Milan (Levi 1987). The study population comprised 357 women with histologically confirmed endometrial cancer, and controls admitted for acute conditions other than malignant, hormonal, gynecological, or smoking-related diseases, diseases associated with factors known to be related to endometrial cancer, or who had undergone hysterectomies comprised the study population. Cases were older, more frequently nulliparous, had greater body mass, were more educated, and had a later menopause. The age-adjusted relative risk for current smokers compared to non-smokers was 0.5 (0.3-0.7); for ex-smokers the risk was 0.8 (0.5-1.4). Dichotomization of amount smoked revealed no dose-response relationship. In contrast to other studies, neither body mass, menopausal status, nor exogenous estrogen use affected the risk estimates.

The study by Tyler, et al (1985) had equivocal results related to the effect of smoking on the risk of endometrial cancer among women under the age of 55. This population-based case-control study involved 437 cases and 3,200 controls selected by random-digit dialing in the same geographic area as the cases. Cases tended to be older, heavier, nulliparous, and to have consumed less alcohol. Relative

risks for current smokers showed a non-significant 20% deficit compared to non-smokers, and did not differ in pack/years smoked. The risk to former smokers was equivalent to that among non-smokers. When risk factors were considered jointly using logistic regression procedures, statistically significantly reduced risks were found for smokers who were post-menopausal or who had used estrogens. While the magnitude of the effect of smoking on lowering risk is not as evident as in other studies, these results do conform well with regard to the modification of risk due to estrogen use and menopausal status. They may also demonstrate, as pointed out by Baron, (1984) that the effect of cigarette smoking may be weaker in the younger age groups composing this study. It should be noted, however, that this study did not consider socioeconomic status, which had previously been found to be related to risk (Elwood 1977).

BREAST CANCER

Results from studies of breast cancer and smoking are less consistent in demonstrating a reduction of risk than those for endometrial cancer. Neither the study by Smith, et al (1984), which found no significant effect of smoking on endometrial cancer, nor the study by Stockwell and Lyman (1987), which found a protective effect, found any significant effect of smoking on breast cancer risk. In contrast, two of the largest prospective studies (Hammond 1966, Doll 1980) found generally lower breast cancer death rates among smokers than non-smokers. In the former study, among women aged 45-64 the ratio of the breast cancer mortality rate in smokers to that in "never-smokers" was 0.8; for heavier smokers that ratio was 0.8. Among women ages 65-79 the corresponding ratios were 1.0 and 1.1.

In the Doll, et al study of female British doctors, the annual breast cancer mortality rate for smokers of 25 cigarettes or more per day was 40 per 100,000 population; for smokers of 15-24 per day the rate

was 73 per 100,000; for smokers of 1-14 per day the rate was 50 per 100,000; and for ex-smokers the rate was 59 per 100,000. All of these rates were lower than the rate of 77 per 100,000 found among non-smokers.

Vessey, et al (1979, 1983) demonstrated a large protective effect of smoking on breast cancer incidence in a study of 1,176 breast cancer patients and age- and parity-matched controls. Cases were married women ages 16-50, whose cancer was newly diagnosed and histologically confirmed. Matching controls were selected from patients admitted for acute medical or surgical conditions or for routine elective surgery. Medical, obstetric, menstrual, contraceptive, and social histories were collected by personal interview. The relative risk for heavy smokers (15 cigarettes or more per day) vs non-smokers was 0.5, and showed a highly statistically significant inverse trend with amount smoked. Adjustment for factors which differed between cases and controls reduced the inverse association slightly (0.7). The authors attributed this unexpected finding to the unrepresentative nature of smoking habits among the hospitalized controls. That is, hospitalized controls would

more likely be smokers than would community controls, resulting in a lower ratio of smoking cases to controls and an apparent protective effect of smoking on the disease. This explanation, however, is not as tenable as for other studies using hospitalized controls since these women were admitted for acute conditions or surgical procedures which probably were not related to their smoking.

O'Connell, et al (1987) used community controls selected from the same catchment area as hospitalized cases in order to avoid this potential selection bias. However, compared to controls the 276 primary breast cancer cases were older, less obese, more educated, and more likely to be nulliparous, have a family history of breast cancer, and not use oral contraceptives. Odds ratios for current smoking, controlling for the potentially confounding effects of age, race, estrogen use, oral contraceptive use, and alcohol consumption were not statistically significantly reduced, but nonetheless showed a significant inverse trend with amount smoked. These risk estimates were 0.8 (0.5-1.1) for current smokers of a pack or less per day, 0.6 (0.3-1.1) for smokers of more than a pack per day, and 1.2 (0.8-1.7) for former smokers. The effect was similar in pre- and post-menopausal

women; 0.9 for pre-menopausal current smokers of 1-20 cigarettes per day, 0.4 for smokers of more than 20 cigarettes per day, and 1.2 for ex-smokers. The respective risks among post-menopausal women were 0.7, 0.6, and 1.1. The apparent negative association might have been due to confounding by body mass, since the cases and controls differed with respect to this variable. Smokers are less obese; obesity is related to late menopause; and both obesity and late menopause are risk factors for breast cancer. However, the analysis indicated that neither body mass index nor age at menopause diluted the apparently protective effect of smoking.

A case-control study of participants in a multi-center breast cancer screening program found a similar, non-significantly elevated risk among former smokers and also among current smokers (Brinton 1986). The self-selected subjects who were interviewed about smoking history comprised 1547 cases and 1930 controls. Of those eligible for the interview, non-respondents among the cases were 15% more frequent than among the controls, primarily because of the death of the study subject. If these deaths were more frequent among non-smoking cases than non-smoking controls, a possible result of a

protective effect of smoking, the estimates of relative risk might be biased toward apparently higher risk associated with smoking. The age-adjusted relative risks for current smokers compared to non-smokers was 1.17 (0.9-1.4), and for former smokers was 1.24 (1.0-1.5). For women who developed breast cancer after age 65, however, there was a non-significantly reduced risk of 0.6 (0.4-1.0). Risk estimates showed no real trend by duration of smoking or by amount smoked, and smokers showed no reduction in median age at menopause. Multivariate analysis controlling for the effect of other potential risk factors had no influence on the lack of an association with smoking. Of course, it is unlikely that analytic control for surrogate measures such as socioeconomic status totally controls for the potential confounding effect of risk factors such as dietary differences, with which they are correlated. The absence of an effect of smoking on lowering the age at menopause is puzzling, given that several studies had previously noted this effect. This may indicate some unknown bias operating in this study which may explain the absence of an inverse association with smoking.

Rosenberg, et al (1984) had similar findings in their study of women ages 30-69, hospitalized with breast cancer, and controls admitted for other malignancies. The control series excluded women with diagnoses of lung cancer, endometrial cancer, or any other cancer associated with smoking or age at menopause. Control patients' diagnoses comprised cancers of the ovary, colon or rectum, or malignant melanoma. Median age of the two study groups was equivalent. The estimated relative risks for current smokers among the 717 cases compared to the 2,160 controls were 1.3 (0.9-1.8) for light smokers (1-14 per day), 1.0 ((0.8-1.4) for smokers of 15-24 cigarettes per day, 1.1 (0.8-1.6) for smokers of 25 or more cigarettes per day, and 1.1 (0.8-1.3) for ex-smokers. A very modest protective effect of smoking could not be ruled out in this study despite its large sample size, although the evidence is against a reduction of 20 percent or more in current smokers. As with the previous study, personal interviews could not be blinded, and the possibility of response or interviewer bias cannot be excluded.

A cohort study by Hiatt and Fireman (1986) similarly failed to demonstrate a protective effect of smoking on breast cancer, despite

the finding that the mean age at menopause was earlier for current smokers. 84,172 women ages 20-84, who were members of a Northern California pre-paid health plan, and who had provided information on smoking habits, were enrolled in this prospective study. Breast cancer cases occurring from 1971-1980 among these women were identified from hospital discharge files and the California Tumor Registry. The mean length of follow-up from the date of entry into the study was 10.5 years. Age-standardized breast cancer incidence rates were 1.27 per 1,000 person-years for non-smokers, 1.38 for current smokers, and 1.63 for ex-smokers. Relative risks were 1.0 (0.8-1.1) for light smokers compared to non-smokers, 1.2 (1.0-1.4) for moderate smokers, 1.2 (0.9-1.6) for heavy smokers, and 1.2 (1.0-1.4) for ex-smokers. The higher risk for moderate compared to heavy smokers, and for ex-smokers compared to both non-smokers and current smokers is curious, and may indicate some related lifestyle factor that occurred differentially between cases and controls, possibly accounting for the lack of a protective effect of smoking. The known risk factor of obesity also was found not to affect risk. The power of this study was sufficient, with 95% confidence to rule out a protective effect of smoking of 5% or more. As to why age at

menopause was inversely associated with smoking and with breast cancer risk, while the risk was still somewhat elevated among smokers, the authors suggest that smoking exerts both a direct, harmful effect on breast tissue and an indirect, protective effect through reduction of estrogen levels.

Schecter, et al (1985) conducted a case-control study among women ages 40-59 who participated in a multicenter breast cancer screening program in Canada. Smoking was found to increase risk twofold among pre-menopausal women who ever smoked, but among post-menopausal women, no overall association was detected. No information on dietary habits was collected, so possible undetected confounding by this factor may explain the finding of excess risk. Similarly, the choice to participate in the screening program may be associated with unknown risk or lifestyle factors which determine or are associated with the development of breast cancer.

Several studies of other breast cancer risk factors also have examined the effect of smoking. Paffenbarger, et al (1979) found that a smaller percentage (52.3%) of cases than medical (55.4%) or surgical (55.7%)

controls reported having ever smoked. This, of course, may not reflect the effect of current smoking on risk. No information was given regarding the diagnoses included in the control groups, nor were the effects of other risk factors taken into account when examining the smoking effect.

Studies of alcohol consumption and breast cancer have indicated correlations between smoking and alcohol use, but have not been consistent in determining the risks of the latter. Recently, Schatzkin, et al (1987) found moderate alcohol consumption to elevate breast cancer risk by 50-100% in a large cohort study based on a sample of the U.S. population. The percentage of women who reported drinking increased with increasing number of pack/years smoked.

In a prospective study of nurses published at the same time, Willett, et al (1987) found a similar risk for moderate alcohol intake, and observed that the association tended to be weaker among women who had never smoked cigarettes. Smoking, itself, was not significantly related to risk. One possible flaw in this study was its failure to determine family occurrence of breast cancer after the subject first

entered into the study, although the subjects were followed for up to nine years.

Harvey, et al (1987) investigated alcohol consumption among 1,799 breast cancer cases and 2,208 controls who participated in the Breast Cancer Detection Demonstration Project. They found a statistically significant trend of increasing risk with increasing average weekly alcohol intake, and an increased risk associated with two or more drinks per day. Although the study suffered from lack of information on dietary habits, the association between moderate alcohol consumption, particularly before age 30, and subsequent elevated breast cancer risk is coherent with other epidemiologic evidence.

A French case-control study (Le Monique 1984) of the effect of alcohol consumption found a relative risk of 1.5 for drinking, similar to a previous U.S. case-control study (Rosenberg 1982), and a small non-significant excess risk associated with current smoking. However, only seven percent of all subjects were current smokers. The observed excess risk from alcohol in these studies might mask the protective effect of smoking seen in some of the studies reviewed

above, since the two factors are highly correlated and have opposite effects on risk.

Another facet of the smoking/breast cancer association was demonstrated in a Japanese study which investigated risk factors associated with multiple primary cancers in breast cancer patients (Kato 1986). Comparisons were made between patients with multiple primary cancers occurring after or concurrently with breast cancer and patients with unilateral breast cancer. A multiple logistic regression analysis indicated that smoking more than 10 cigarettes per day significantly decreased the risk of multiple primary cancers (RR=0.23). Risk factors for breast cancer in general also tended to increase the risk of second primaries. Since medical records were used to obtain smoking histories, and it is not clear how accurate these records are in Japan, these results are open to some doubt.

None of these studies considered differences between estrogen receptor (ER)-rich and (ER)-poor breast cancers and differences in the risk factors for each. If the mechanism by which risk factors for the disease operate is associated with alteration of the ER status of

the cells from which the cancer develops, and if the ER status of the fully-developed tumor reflects the receptor status of the original cells, ER-rich and ER-poor tumors would differ with respect to those risk factors. Differences in ER status between populations being compared could, therefore, account for some of the differences in the results from the studies discussed above. McTiernan, et al (1986) calculated relative risks for ER-rich and ER-poor breast cancers with respect to known breast cancer risk factors. They found several factors which were risk factors for one type but not the other. Cigarette smoking was not found to be a statistically significant risk factor for either type, although it reduced the risk of ER-poor tumors by 25% among current smokers and 16% among ex-smokers, compared to non-smokers. Essentially no difference was found for ER-rich tumors.

CONCLUSIONS

As previously discussed, consistency of results upon replication is strongly indicative of a causal relationship, particularly with differing study designs and populations. Similarly, consistency of results indicating a reduced risk among an exposed population strongly supports a protective effect due to that exposure. In the case of endometrial cancer and smoking, the consistent inverse dose-response relationship is evident and the close concordance of risk estimates among studies is remarkable. Clearly, the risk of endometrial cancer among smokers is half as great as that among non-smokers. This relationship appears to be affected by body weight and by exogenous estrogen use, as well as by menopausal status. The protective effect of smoking exerts itself more strongly among post-menopausal women and those who weigh less. It appears to cancel the increased risk due to usage of exogenous estrogens, particularly among long-time users.

While estimates of the actual incidence of endometrial cancer are imprecise due to misclassification, there does appear to be an

epidemic of the disease during recent years. The increasing incidence probably is due to increasing use of estrogen replacement therapy, although it may in part reflect better case-finding and changing diagnostic criteria. Smoking is likely to be a powerful moderating factor of this rise.

The inconsistency of results from epidemiologic studies of breast cancer risk due to cigarette smoking is undoubtedly due to the complex etiology of the disease. Additional research aimed at unraveling the specific hormonal components and mechanisms affecting the occurrence of the disease is needed. A role for smoking in lowering the risk of the disease is highly plausible, despite the varied results of the studies reviewed herein, because of strength of the findings in endometrial cancer studies of a relation to estrogen levels and to the additional avenue of weight reduction as a protective factor. The breast cancer/smoking results, by their inconsistency, exemplify the potential misinterpretation of epidemiologic studies that do not consider molecular, cellular, metabolic, or other unascertained differences among comparison subjects, such as

alcohol consumption, and differences in the effect of cigarette smoking on estrogen receptor-rich and ER-poor tumors.

Finally, it is worth conjecturing that in males the risk of other hormonally-dependent diseases, such as prostate cancer, might be reduced by smoking. Certainly, this subject should have been studied, but reports are absent from the literature.

COLON DISEASES

COLON CANCER

There is suggestive evidence in the literature of a protective effect of cigarette smoking on the risk of colon cancer. Over twenty years ago, Hammond (1966) found that the colon cancer mortality rate among women smokers ages 45-64 was 78% that of women who had never smoked cigarettes regularly. "Heavier" smokers had only about two-thirds the mortality rate of never-smokers. Among males in the study, no significant effect of smoking was noted. Data from the Framingham study support an inverse relationship between smoking and colon cancer incidence (Williams 1981). Fifty-eight colon cancer cases occurred among the 5,209 participants; 28 among males and 30 among females. A logistic regression analysis revealed a statistically significant inverse association between smoking level and colon cancer in both sexes. Smokers of a pack or more per day almost one quarter the rate of colon cancer as did non-smokers.

The population-based Third National Cancer Survey found that the relative odds of colon cancer for smokers compared to non-smokers were about 25% lower for males and 10% lower for females (Williams

1977). Among Japanese in Hawaii, the relative risk of colon cancer was found to be reduced by a third for male smokers of a pack or more per day compared with smokers of less than that amount and slightly reduced for tobacco users compared to non-users.

Only one study has focused specifically on the relationship between cigarette smoking and colorectal cancer (Sandler 1988). This study was a prospective follow-up of disease incidence over a 12-year period among over 25,000 women in Washington County, Maryland. Incident colorectal cancers were obtained from a county-wide registry and matching of residents' death certificates against the initial study population census provided the remainder of the cases. The census also provided information on smoking habits and demographic characteristics. The relative risk of developing colorectal cancer for ever smokers compared with non-smokers was significantly reduced (RR = 0.3, 0.2-0.4).

Age-adjustment eliminated the statistical significance of the reduced risk, however, after adjustment for differences in other factors, the relative risk for women smokers over age 50 again was reduced

(RR=0.6, 0.4-1.0). Age-specific relative risk suggest that the apparent protective effect of smoking on colorectal cancer risk in women is stronger at old ages. This may reflect partial mediation by the antiestrogenic effect of which showed that the incidence of colon cancer in women with children was 30%-50% less than in nulliparous women.

Few other studies have evaluated the effect due to smoking, and it is possible that lifestyle factors which increase the risk of colon cancer and which are independently associated with smoking, may mask its possible protective effect. Apparently, alcohol is one of these factors. Wu, et al (1987) in a prospective study of almost 12,000 residents of a retirement community found a twofold increase in colorectal cancer risk for daily alcohol drinkers. This excess reached statistical significance in males, but not in females. The study also indicated another possible factor which might mask a protective effect of cigarette smoking; i.e., body mass. This factor, as measured by Quetelet's index, was associated with elevated risk of colorectal cancer and is known to be inversely related to cigarette usage, as discussed previously.

ULCERATIVE COLITIS

Ulcerative colitis is a recurrent inflammatory and ulcerative disease of the colon and rectum, characterized clinically by rectal bleeding, diarrhea, abdominal pain, anorexia and weight loss (Kirsner 1982). Patients with total ulcerative colitis lasting longer than seven years are at increased risk for carcinoma of the colon and rectum, which develop earlier, and with a tendency toward multiple lesions.

A large body of evidence from epidemiologic studies conducted during the past decade demonstrates that the risk of ulcerative colitis is reduced among persons who smoke cigarettes. For example, the disease occurs more frequently among Mormons, who generally refrain from smoking (Penney 1983). More importantly, the remarkable concordance in the magnitude of the reduced risks observed in numerous studies, despite their different designs and study populations, lends plausibility to this hypothesized association, although the specific biological mechanisms for this phenomenon have not yet been confirmed.

Other scientific evidence, though possibly limited generalizability, dramatizes the inverse association. De Castella (1982) reported on a female who smoked a half-pack or less per day for fifteen years. Upon stopping at age 33, she developed ulcerative colitis, but when she started smoking again some nine months later, her symptoms disappeared within four weeks. Within five weeks after restarting eighteen months later, the symptoms reappeared. After five months she resumed smoking and they disappeared. A third time she stopped, and the symptoms reappeared, only to disappear again when she resumed smoking three months later. She attempted to stop twice more, with the recurrence of symptoms. She now smokes, as condoned by her medical advisors, and "remains well."

Roberts, et al (1982) reported on a woman who developed colitis in 1961. When she started smoking in 1964, the symptoms of the disease disappeared. Seven years later she stopped smoking and thereafter, relapsed. Her symptoms disappeared when she began smoking again. She repeated this several times with the same results. Currently, 16mg per day of nicotine (gum) maintains her remission.

As interesting and suggestive as these anecdotal reports are, epidemiologic studies provide the incontrovertible evidence of an inverse association between smoking and colitis. Harries, et al (1982) conducted a case-control study, using questionnaires mailed to colitis and Crohn's disease patients (cases), and to controls who had attended a fracture clinic and who were matched for age and sex, but not socioeconomic status, to the cases. The study population comprised 230 ulcerative colitis patients, 190 Crohn's disease patients, and 230 controls. 8% of the colitis patients, 42% of the Crohn's disease patients, and 44% of the controls were current smokers. The difference in the proportion of smokers among the colitis patients compared with the other groups was highly statistically significant. 48% of the colitis patients had never smoked, compared to 30% of the Crohn's disease patients and 36% of the controls. These differences also were statistically significant. 40% of the colitis patients were ex-smokers, averaging 13 years since stopping. Only 27% of the Crohn's disease patients and 20% of the controls had quit. Part of this apparently increased risk to ex-smokers might have been due to significantly more (76%) of the

patients with colitis coming from non-smoking households compared to the Crohn's disease patients (60%) and the controls (51%). Among colitis patients, 82% of non-smokers came from non-smoking households, whereas 78% of the smokers came from smoking households.

Jick and Walker (1983) selected ulcerative colitis patients and controls from data collected previously in a multinational study of some 45,000 patients, and in a study of some 25,000 patients admitted to Boston area hospitals. Data from a total of 239 colitis patients and 956 controls were reviewed for information on patients' smoking histories. Overall, the risk of ulcerative colitis in current smokers was 0.31 (0.22-0.43) compared to non-smokers. The lower risk was present in every age group, with more reduction in men than in women and more in heavier than in lighter smokers. In both sexes, there was little additional reduction in risk associated with smoking more than 1 pack per day. For ex-smokers, the risk was 1.16, though not statistically significant. The lowered risk among current smokers was present in both studies, and in each country in the multinational effort. The rather low relative risk for current

smokers might, in part, be due to the exclusion from the control group of persons with diagnoses of cancer, cardiovascular disease, or respiratory illnesses.

A small Czechoslovakia study found somewhat higher risk estimates, although the methodology and statistical analyses were not reported in detail (Bures 1982). Odds ratios for male colitis patients compared to male Crohn's disease patients were 0.4 for current smoking and 1.0 for non-smoking. In females, the respective were odds ratios 0.5 and 1.2. The authors also examined data from 22,060 autopsies conducted over 20 years, and discovered twice as many smokers as non-smokers among Crohn's disease subjects, and half as many in ulcerative colitis subjects. Another small study showed somewhat higher proportions of smokers in each group, but had an equivalent relative risk; i.e. 10 of 40 colitis patients smoked compared to 22 of 35 Crohn's patients (Entrican 1986). These findings, though similar to those from other studies, must be viewed with caution because of the limited information contained in the reports.

Holdstock, et al (1984) interviewed 102 outpatients diagnosed with ulcerative colitis, 96 with Crohn's colitis, and 54 with Crohn's disease of the small bowel. Only 8% of the colitis patients smoked, compared with 25% of the Crohn's colitis patients and 52% of the small bowel Crohn's disease patients. The respective proportions of ex-smokers were 32%, 30% and 13%. However, the large differences between colitis and Crohn's disease patients are somewhat misleading with regard to risk, since most studies indicate increased risk of Crohn's disease in smokers. A better comparison group would be persons not having inflammatory bowel diseases, although a particular design, such as used in a recent study might not allow this (Cope 1986). Here, colonoscopy patients were interviewed, then divided into an ulcerative colitis group and a control group (the latter containing persons diagnosed with diverticular disease, irritable bowel syndrome, colonic carcinoma, or colonic polyps). 13% of the case group were smokers while 42% of the controls currently smoked.

The magnitude of the reduced risk among smokers was slightly less in a recent study from Milan which avoided a comparison between

colitis and Crohn's disease patients (Franceschi 1987). In this hospital-based investigation, cases included both ulcerative colitis and Crohn's disease patients, while controls were hospitalized for acute conditions, and those with tobacco-related, malignant, respiratory, or digestive diseases were excluded. The estimated relative risk of colitis in current smokers was 0.6 (0.3-1.0) with a significant trend of lower risk associated with greater amount smoked, and of lower risk with longer duration of smoking. Among ex-smokers, the relative risk was 2.6 (1.4-4.6). In contrast, among patients with Crohn's disease, both current and ex-smokers had relative risks significantly greater than unity (3.2 and 3.9). While 26 of 46 ex-smokers with colitis quit after the first appearance of symptoms, only 4.3% cited "abdominal disturbances" as the reason. Heavier smokers quit more frequently than did light smokers, but quitting was not associated with appearance of symptoms. Because the control group in this study excluded patients with diseases thought to be related to tobacco use, a necessary methodological consideration in any hospital-based investigation, its risk estimates are probably more precise than the studies previously reviewed here. However, population-based studies are preferable, so that a trade-off

between artificially under-representing or over-representing smokers among controls does not have to be made.

Logan, et al (1984) and Somerville, et al (1984) used case-control designs for studying smoking among patients with ulcerative colitis or Crohn's disease. In the former, questionnaires were mailed to 124 patients and for each case to two controls who were selected from the records of each case's physician, and matched by age and sex to the case. The relative risk for non-smokers compared to current smokers was 3.8 (2.0-6.9); the association remained when smoking status prior to three months before the onset of clinical disease was used. In the latter, a case-control study of Crohn's disease, relative risks of 4.0 (1.9-8.1) for ever-smoked, 3.5 (1.8-6.6) for current smokers, and 4.8 (2.4-9.7) for smokers at time of disease onset were found.

Similarly, Tobin, et al (1987) sent questionnaires to 280 patients (143 ulcerative colitis, 137 Crohn's disease) and an equal number of age- and sex-matched community controls. Great care apparently was taken to avoid information bias, particularly in framing the questions regarding smoking habits. The relative risk for colitis among

current smokers at the time of the interview was lower than any previous study, 0.2 (0.1-0.3). The relative risk was equivalent for smoking status at the onset of symptoms. The risk for ex-smokers was greater than for non-smokers, 1.5 (0.8-2.8), but was not statistically significantly higher. In contrast, among Crohn's disease patients, the risk for current smokers was 1.9 and for ex-smokers was 1.6, though neither was significant. There was a significant trend of decreasing relative risk associated with increasing amount smoked per day. 76% of ex-smokers with colitis stopped before onset. Results for a case-control study by Benoni and Nilsson (1987) which compared patients having inflammatory bowel disease with community controls found reduced risk of ulcerative colitis and elevated risk of Crohn's disease for current smokers which were of the same magnitude as those of Tobin, et al. A more recent Swedish study (Lindberg 1988), which used a similar study population, found a statistically significantly reduced colitis relative risk of 0.7 for smokers compared with never smokers. In this study, ex-smokers had a significantly elevated relative risk. The risk of Crohn's disease was elevated for current and former smokers, although only the former reached statistical significance. It is

possible in these two studies that differential selection of cases and controls (i.e. cases from a hospital population, controls from the community) might have resulted in over-representation of smokers among cases. Nonetheless, the results of Tobin, et al (1987) confirm others' observations that associations with smoking antedate the onset of inflammatory disease (Franceschi 1987), and that they are, therefore, more likely to be protective.

Boyco, et al (1987) seem to have overcome some of the aforementioned problems of previous hospital-based studies by selecting both cases and controls from enrollees in a Health Maintenance Program, and by eliminating subjects with Crohn's disease. 250 subjects with colitis or proctitis, and an equal number of age- and sex-matched controls were selected from an overall population of 304,000. Telephone interviews were conducted to obtain smoking histories. The estimated relative risk of ulcerative colitis was 0.6 (0.4-1.0) for current smokers (at the time of onset of symptoms) vs never-smokers; and 2.0 (1.1-3.7) for ex-smokers vs never-smokers. The magnitude of these risks was unchanged by adjustment for coffee or alcohol consumption. Among current smokers, relative risks for 1-20

pack/years were not significantly different from unity, but the RR for 21 or more pack/years was 0.5 (1.3-17.6). Among ex-smokers the excess risk was also significant in this duration category. In addition, the authors reanalyzed data from two previous outpatient studies (Harries 1982 and Logan 1984) and one inpatient study (Jick 1983) to assess the risks to ex-smokers. They found agreement in the estimated relative risks with their own estimates, although the risks in the Jick study were slightly lower, perhaps due to over-representation of former smokers among controls. (This may be similar to the recognized over-representation of present smokers in hospital populations). It has been suggested that differential response rates between cases and controls (85% vs 62%) might explain the Boyco, et al (1987) findings if smokers were over-represented among the non-responders (Logan 1987). It has been found that non-respondents are more likely to be smokers (Criqui 1978). More recently in a similar study Sandler and Holland (1988) sent questionnaires to inflammatory bowel disease cases drawn from the rosters of three chapters of the National Foundation for Ileitis and Colitis and to neighborhood controls. Their findings with regard to ulcerative colitis also were similar; i.e. a significantly decreased

odds ration (0.5, 95% CI=0.3-0.9) with the lowest risk found for the heaviest smokers.

Of course, dietary habits could conceivably confound or partially explain these results. Thus, Thornton, et al (1980) compared dietary histories of 30 colitis patients and fracture clinic controls. They failed to find any significant differences, (in contrast to their previous study of Crohn's disease patients), indicating that Crohn's disease and ulcerative colitis "despite their similarities, ...do not have identical etiologies." A later study of 30 patients with colitis, 30 with Crohn's, and two groups of matched controls from a fracture clinic demonstrated no difference between smokers and non-smokers with regard to dietary habits, although compared to controls the Crohn's patients consumed more refined sugar whereas no difference was noted for the colitis patients (Thornton 1985). Katschinski, et al (1988) confirmed the positive association with refined sugar intake, although excess risk was evident only in ex-smokers and never-smokers.

A small prospective study by Vessey, et al (1986) of white married women ages 25-39 determined an overall incidence of ulcerative colitis of 0.15 per 1000 person/years and to 0.09 for Crohn's disease. Respective incidence rates in smokers were 0.11 (0.16 for 1-14 per day, 0.04 for >14 per day) and 0.17; in non-smokers they were 0.17 and 0.05. Incidence rates in ex-smokers were the same as in non-smokers for both diseases. Most importantly, the information on smoking habits was collected well prior to the onset of symptoms, making it highly unlikely that the disease influenced the women's smoking habits.

Certainly, the apparently increased risk of ulcerative colitis in ex-smokers and of Crohn's disease in current smokers is puzzling. One explanation for the increased colitis risk in ex-smokers contrasted to the decreased risk in current smokers is that the act of stopping smoking predisposes individuals to ulcerative colitis (Kennedy 1984, Amery 1984). Logan and Langman (1984) explored this hypothesis in their and others' data, finding no consistent supportive evidence. The results from Tobin, et al (1987) and Boyco, et al (1987) suggest that the apparently increased risk in ex-smokers might be artifactual, while a more recent study of colonic mucous production in vitro

indicates that cessation of smoking disrupts the capacity of the normal colon for production of mucous (Cope 1988). The excess risk of Crohn's disease, however, appears real. Holdstock, et al (1984) suggest that smoking influences pathological appearances, perhaps by affecting the immune system, resulting in features of Crohn's disease rather than colitis.

Tobin, et al (1987) hypothesize that smoking might influence which disease develops in persons with genetic predisposition to inflammatory bowel disease. An explanatory biological mechanism for these suggestions remains elusive, although a mechanism for the observed colitis/smoking inverse relationship, i.e. a protective effect due to colonic mucus, seems quite plausible. In tissue culture, biopsied specimens from colitis patients had significantly less incorporation of tritiated glucosamine into colonic mucus. Non-smoking colitis patients showed reduced mucus production compared to non-smoking controls, while colitis patients who smoked had similar mucus production to that of all controls.

Of course, some cause of ulcerative colitis might explain the observed association. Struck by the similarity of the inverse relationship in both Parkinson's disease and ulcerative colitis, Bihari and Lees studied twenty-five patients with both of these diseases (Bihari 1987). 20 never smoked, 3 were ex-smokers for a long time, 1 smoked a pipe occasionally, and 1 smoked 10 cigarettes per day. The authors call for prospective epidemiologic studies to determine whether persons with these two diseases, rather than sharing protection by smoking, instead share a "distinctive premorbid personality". This is unlikely, however, given the results of Monk, et al (1970) who, in a study of 193 ulcerative colitis patients, failed to determine psychological factors which were important in the development or continuation of the disease. Also, Helzer, et al (1982) conducted a personality assessment and tabulation of recent stressful events on fifty colitis patients and matched non-gastrointestinal controls, and found no greater frequency of diagnosable psychiatric disorder in the former. Personality profiles also were similar. Nor were significant differences found in comparisons between colitis and duodenal ulcer patients with regard to obsessive personality traits, although the colitis group worried more about their disease. No sociocultural

factors were measured, although these are known to influence obsessive scores, and to be somewhat related to the disease, i.e. patients having higher educational and economic level than general population controls (Bellini 1976).

The scientific literature linking cigarette smoking to a significant reduction in the risk of ulcerative colitis is impressive for its congruence and the absence of other rationale explanations for this observation. While many may view this possible benefit of smoking as inconsequential in relation to its perceived overall effect on mortality, it is important to also consider how, in this case, smoking can improve the quality of life. Its affect appears to be strongest for current smokers, and may, in fact be limited to this group. Anecdotal reports imply reversibility of the protective action, with rapid effect. Missing is clear evidence of a plausible biological mechanism. Because of the speedy effect of smoking in ameliorating the symptoms of the disease, research to discover a mechanism for its action should be comparatively straightforward.

PARKINSON'S DISEASE

The annual incidence of Parkinson's disease in the U.S. was estimated to be 16,000 - 36,000 new cases, with a (point) prevalence of 140,000 - 360,000 cases (Kessler 1973). Although the etiology of the disease is largely unknown, hence the designation idiopathic Parkinson's disease (IPD) for the most common variety of Parkinson's syndrome, results from most epidemiologic studies of IPD demonstrate an inverse relationship between IPD and cigarette smoking.

Prospective follow-up studies of British doctors (Doll 1976, 1980), U.S. veterans (Kahn 1966) and over one million people in 25 states (Hammond 1966), found lower mortality rates from Parkinson's disease among persons who ever smoked compared to those who never smoked. Relatively few subjects in these studies developed Parkinson's, but in each investigation, the relative risk of mortality from IPD was lower in smokers. Of course, these studies are somewhat limited because Parkinson's disease is not usually an immediate cause of death and its reporting on death certificates is

unreliable. Thus, these prospective studies do not give the complete picture of the relationship between smoking and PD. Furthermore, no data on temporal sequence or potentially confounding factors were available.

Case-control studies provide larger numbers of IPD subjects, and therefore, more precise risk estimates, although the potential for bias is greater. Early community and hospital-based studies by Kessler (Kessler 1972a, 1972b, 1973) confirmed the findings from the prospective studies. More recently, Rajput, et al (1987) compared smoking histories of 64 female and 54 male cases with those of 128 female and 108 male controls. 45% of the controls reported having ever smoked, compared to 37% of cases; a result suggestive of an negative relationship, but not statistically significant (OR = 0.7, 95% CI = 0.4-1.2). Former smokers were more frequent among cases than controls (24% vs 19%), but current smokers were twice as frequent among controls than cases (26% vs 13%). The relative risks for ever-smokers compared to never-smokers decreased with increasing age, ranging from 2.5 for the 45-59 age group to 0.3 for the 80+ group. Neither the relative risks nor the trend were statistically significant.

The mean age at diagnosis was significantly older for the never-smoked group than for the ever-smoked group. Since smoking history was obtained at the time of diagnosis, and inability to recall previous smoking habits may be associated with the disease, recall bias might have been present.

Godwin-Austen, et al (1982) conducted a case-control study of 350 pairs of Parkinson's patients and matched controls. An odds ratio of 0.5 for current smoking vs non-smoking was found to be statistically significant. The risk was the same regardless of whether smoking status at the time of diagnosis or 20 years earlier was used. Relative risks for ex-smoking vs never smoking decreased from 0.8 for those who quit 10 years before diagnosis, to 0.6 for those who quit 1-10 years before diagnosis.

In a Finnish case-control study of 443 Parkinson's disease patients and age- and sex-matched controls, 73.6% of the PD patients had ever smoked compared to 67.3% of the controls, a statistically significant difference (Marttila 1980). Furthermore, of the 117 PD patients who had smoked, 76.1% had stopped, while in the control series,

significantly fewer (53.8%) had quit. However, the report does not mention when, in relation to the onset of symptoms, these persons quit smoking.

Baumann, et al (1980) compared smoking histories of Parkinson's disease patients and matched controls selected by door-to-door canvassing of the cases' neighbors. Because of this selection process, cases and controls were equivalent in terms of socioeconomic status and marital status, in addition to age and sex, for which they were matched. Information on coffee and alcohol consumption was collected and in both groups the percentages who had at some time regularly consumed coffee or alcoholic beverages were equivalent. Cases tended to begin drinking both beverages at a significantly earlier age than their neighbors. Of the Parkinson's disease patients, 63% had never smoked cigarettes regularly, compared to 47% of the controls; a statistically significantly reduced odds ratio of 0.46. This significant difference was evident for smoking status 20 years before symptoms onset, 10 years before, and just before onset. One explanation for these results, i.e. selective mortality of smoking Parkinson's patients could not be supported by the information

collected on deceased patients, nor by differential proportions of smokers among patients with different disease durations. Nicotine exposure was determined from information on brands smoked, and was not significantly different between cases and controls.

Golbe, et al (1986) failed to find an inverse dose-response relationship between several measures of disease severity and cigarette usage in a study of 32,000 of the United Parkinson Foundation members. The study was irreparably flawed because the underlying hypothesis, i.e. "that patients with PD who have smoked should have milder disease and/or a late onset of symptoms than lifelong non-smokers," does not rule out a protective role for cigarette smoking. Furthermore, the scientific literature contains numerous examples which demonstrate that the age-of-onset for a disease may not be dose-related, even though the risk of the disease is thus related. Thus, while it appears from this study that the rate of disease progression and the age at diagnosis are unrelated to smoking status among people with PD, the study presents no evidence that smokers are more or less likely than non-smokers to get the disease in the first place.

One case-control study (Rajput 1984) failed to confirm the inverse relationship between smoking and PD. In this study, medical records of Olmsted County, Minn., residents during 1967-1979 were reviewed for evidence of Parkinson's disease. For each case, the next two medical facility attendees matching the case in age and sex were selected as controls. Information on smoking habits and other illnesses was abstracted from the medical records. Approximately 55% of the controls and 52% of the patients never smoked. Controls reported significantly more hypertension and significantly less psychoneuroses and psychosomatic illnesses. However, information on tobacco usage is not reliably obtained from medical records, and controls selected from medical populations tend to include more smokers. Furthermore, the comparison populations in this study clearly were different in a number of factors which could have confounded the results, as manifested in differential hypertension prevalence. These factors probably account for the disparate findings.

In studies with small numbers of subjects, the consistency of results across studies is a good indicator of the validity of an hypothesized relationship. In the aforementioned studies the magnitude of the risks is relatively consistent; risks are lower for current, as opposed to former smokers; and alternative explanations for studies' observations are comparatively unlikely. Furthermore, reasonable biological mechanisms exist for explaining how smoking could prevent or ameliorate Parkinson's disease or its symptoms. Most favored among these is the facilitation of dopamine release and dopaminergic neural transmission through chronic nicotine exposure (Baron 1986). (Most idiopathic parkinsonism features depletion of dopamine in the basal ganglia.) The findings of Baumann, et al (1980) and Haack, et al (1981) of no relation between nicotine exposure and the severity of disease among PD cases argues against this, but Haack, et al based their inferences on observations of cases only, and mistakenly assumed that the severity or age-at-onset of a disease necessarily correlates with the magnitude of an exposure. In any event, nicotine exposure determination has been shown to be rather imprecise (Gori 1986). Alternatively, it has been hypothesized that smoking lowers monoamine oxidase B (MAOB)

activity, thus reducing the conversion of non-toxic precursors into a specific neurotoxin for dopaminergic nigrostriatal neurons. This hypothesis has received considerable attention recently with the finding of a nicotine-like pyridine derivative (MPTP) contaminating some illicit drugs, which, after conversion into MPPT by MAOB, kills these neurons and produces lasting symptoms of Parkinson's disease in humans and lower primates. However, Yong and Perry (1986) measured MAOB in autopsied brain tissues of PD patients and in adult controls dying without PD, and found enzyme activities similar. They did, on the other hand, find that MAOB activity in platelets of heavy smokers was significantly lower than that in non-smokers. In an experimental study, they found that hydrazine, a substance found in tobacco smoke, protected dopaminergic nigrostriatal neurons in mice from damage by MPTP.

Other possible mechanisms include blocking the uptake of (MPP^+-like) toxins into dopamine neurons by pyridines contained in cigarette smoke (Javitch 1984, Snyder 1985), creation by carbon monoxide of a reducing environment that protects the substantial nigra from oxidative damage (Calne 1983), or enhancement of the

metabolism and elimination of toxic compounds by induction of cytochrome P450 systems in the liver or elsewhere (Baron 1986). These mechanisms require continued cigarette smoking, and thus are consistent with the evidence from Rajput, et al (1987) and Godwin-Austen, et al (1982), showing a lower risk for current smokers versus former smokers.

Other independent evidence, such as lower incidence of Parkinson's in blacks, (who smoke more than whites) and the apparently increasing number of cases occurring in younger age groups, (where the proportion of smokers has been decreasing) (Teravainen 1986) lends credence to this inverse association. There are, however, alternate, though somewhat unlikely, explanations for these findings. It is possible that persons predisposed to Parkinson's disease do not begin smoking because of sensitivity to the negative effects of repeated nicotine on metabolism (Maker 1987). Thus, the reason why fewer smokers appear among Parkinson's patients is that they, to a greater extent than non-predisposed persons, are unable to begin the smoking habit. This predisposition hypothesis implies an early familial or environmental influence on the etiology

of the disease, a genetic component such as that which has been raised ever since James Parkinson first described "Paralysis Agitans" in 1817 (Barbeau 1982), or that "premorbid non-smoking in parkinsonian patients is simply an epiphenomenon of a premorbid PD personality type" formed before adolescence but not hereditary (Golbe 1986, Duvoisin 1981).

Several studies among twins clearly indicate no genetic component. Duvoisin, et al (1981) found zero concordance for Parkinson's disease among 12 monozygotic twin pair volunteers solicited through physicians and PD organizations in New York. In this study, 2 twins with Parkinson's disease (probands) and 5 twins without PD (co-twins) were current smokers. 4 probands and 1 co-twin were ex-smokers. Co-twins smoked for a longer period of time and more heavily, though none of the smoking differences approached statistical significance. Ward, et al (1983) studied 65 pairs of twins and a set of quadruplets, similarly solicited, and found a PD concordance rate of between 2% and 5%, depending on interpretation of inclusion criteria. They failed to find any postnatal etiologic factor, although they did confirm the differential smoking habits found by

Duvoisin, et al. Further analysis of these twin pairs which concentrated on those discordant for PD found no statistically significant difference in possible environmental determinants. The only significant result was less cigarette smoking by those with Parkinson's disease.

One possible explanation for the observed inverse relationship is that PD may be under-reported as a cause of death in persons known to be smokers, simply because a suspected smoking-related cause of death would be more likely to be assigned. So, in mortality studies utilizing underlying cause of death, Parkinson's disease would be more likely to appear as a cause of death among non-smokers than smokers; spuriously resulting in an inverse relationship between the disease and smoking. Results from incidence studies (Godwin-Austen 1982), however, argue against this conjecture.

A clearcut beneficial effect of cigarette smoking is strongly supported by the scientific literature, although it is possible that this effect is spurious for reasons similar to those affecting studies demonstrating harmful effects. The effect appears in long-term incidence studies

aimed at describing the detrimental effects of smoking, and in retrospective case-control studies directed specifically on investigating the protective effect of smoking noted previously in those prospective investigations. No obvious alternative explanation for these findings is supported by scientific evidence. Godwin-Austin, et al (1982) demonstrated the required temporal sequence, so it cannot be argued that the observed inverse relationship is due to PD patients selectively quitting smoking. No potential confounding factor which is associated with smoking and is predictive of PD has been identified. The results from prospective studies eliminate information bias due to underreporting of smoking by PD patients, and over-representation of smokers in control groups as reasons for the observed relationship and several possible biological mechanisms have been proposed. Additional research to identify the actual mechanism would be fruitful. The effect of smoking on reducing the incidence of Parkinson's disease is particularly tantalizing given the recent suggestions (Lewin 1987) that the disease is occurring at earlier ages. While this shift in age at onset might be due to increased exposures to some environmental hazard, one cannot easily dismiss the possibility that the recent reductions in the

proportions of younger smokers might in part be responsible for these recent observations.

OTHER DISEASES AND CONDITIONS

Although uncommon and accounting for about 1,300 deaths in the U.S. per year, cancer of the extrahepatic bile duct is another neoplastic disease which appears to be both hormonally related and less frequent in cigarette smokers. A recent epidemiologic case-control study (Yen 1987), which represents the best effort to-date to describe the etiology of the disease, comprises only 67 patients. Information on smoking, alcohol consumption, oral contraceptive use, and medical history was obtained by person interview of these patients and was compared with similar information obtained from 273 control patients with other ("non-tobacco-related") cancers. Compared to non-smokers,the rate ratio for current smokers was significantly reduced (RR=0.4, CI=0.18-0.86), and the rate ratio for ex-smokers was half that of non-smokers, though marginally non-significant. No differences in consumption of alcohol or other beverages between cases and controls was found. Histories of oral contraceptive use and of ulcerative colitis were statistically significantly associated with increased risk of extrahepatic bile duct cancer. The association with ulcerative colitis is interesting and

consistent with the extensive evidence of a protective effect of smoking in the causation of the disease. One might expect the apparent protective effect of smoking on extrahepatic bile duct cancer to be stronger since the inverse relationship was especially prominent for "smoking-related" cancers, with a relative risk of 2.0 (1.3-3.0) for the lowest compared to highest quintile.

NICOTINE AS A BEHAVIORAL AID

Warburton (1987) has argued elegantly for adoption of a functional view of smoking as a way to control one's psychological state; that is, as a benign form of self-medication rather than an irrational habit. He cites numerous studies of smoking motives and situations which support this functional model, and which indicate intrinsic constitutional differences between people who choose to smoke and those who do not. The functional view that smoking is the outcome of the interaction between a person and a situation derives from this evidence. The variation of one's smoking behavior in response to stressful events demonstrates the usefulness of smoking as a method of personal control of one's psychological state, and also of the efficiency of smoking as a nicotine delivery system providing rapid positive feedback. Studies of smoking cessation provide additional support for the functional view of smoking because they demonstrate that ex-smokers report an increase, after abstinence, in the effects they claim to avoid by smoking.

In several respects the effects of nicotine are similar in animals and humans, although the tissue distribution of nicotine differs among animal species and has not been determined in humans (Svensson 1987). In humans and animals, the drug has been found to have both

a depressant and a stimulant action, depending on dosage and time after administration. Furthermore, based on animal experiments it appears that tolerance to the rewarding effects of nicotine does not develop (Iwamoto 1987). This, of course, most unexpected. Clark (1987) recently reviewed the evidence from animal studies which corroborates the theoretical and clinical evidence of the effects of nicotine on humans. He cites studies which have found decreased aggressive responding in humans and squirrel monkeys, depression of the consumption of sweet-tasting high-caloric foods in humans and rats, and improved mental performance and discrimination behavior in humans and rodents. Furthermore, he indicates that several of the behavioral actions of nicotine in animals are consistent with the effect of nicotine in alleviating anxiety and improving performance in humans.

Pharmacological experiments of the effects of nicotine on humans are of varied quality because of the methodological difficulties and ethical considerations inherent in this type of research. Individual variability and a complex relationship between habituation, perception, expectation, and personal control of dosage make interpretation of behavioral research on nicotine rather difficult. Nevertheless, the beneficial effects of nicotine on a variety of aspects of performance are well-documented in the scientific literature. Among the direct benefits are improved performance on certain

tasks; skeletal muscle relaxation; stress, anxiety, and pain reduction; central nervous system arousal; appetite suppression and weight reduction, memory improvement; and mood elevation (Pomerleau 1986, Warburton 1986, Clark 1987, Domino 1987). These effects may be classified as improvements in 1) Vigilance, 2) Learning and memory, 3) Problem solving, 4) Motor control, and 5) Control of response to stressors. Although some of these effects clearly are inter-related, e.g. problem solving involves both attention and memory, this classification provides a useful framework for presenting the scientific literature on nicotine as a behavioral aid.

This presentation is not intended to be a comprehensive review, as several excellent reviews of the subject already are in the literature (Wesnes 1983). Rather, specific articles will be cited as examples of the evidence for or against a particular behavioral effect of nicotine. The reader should be aware of the numerous experimental parameters which affect the validity of this evidence. For example, the experimental approaches used in these investigations required the voluntary cooperation of a few subjects in a rigid controlled setting. Thus, the ability to generalize the studies' results may be limited, and one can question how well performance on tasks contrived for the experimental setting relates to the normal experience. Furthermore, timing is of critical importance in these studies because in general a pulse of relatively concentrated nicotine

reaches the brain rapidly, it is rapidly diluted and has a very short biological half-life. In fact, there are so many places for significant variation in experimental design among studies that comparisons cannot easily separate real differences in their results from spurious ones due solely to different study designs.

Vigilance actually involves three distinct aspects, namely sustained attention, selective attention, and distraction avoidance. Testing of vigilance usually involves having a subject monitor a signal source for some unpredictable variation or specific sequence. The types of vigilance tests which have been employed vary widely, with the ideal being, as noted by Wesnes and Warburton (1983), a task in which one can demonstrate in a short testing period both impairments and improvements over time. Among the classic experiments are measurements based on the Continuous Clock Task (Macworth 1965) in which subjects are required to detect a brief pause in the passage of the second hand, and the "letter crossing test" (Wittenborn 1943) or its derivatives (Bakan 1959) which require picking out specific sequences. These tests measure sustained attention, and nicotine has been found to improve performance. In one experiment using the continuous clock method, heavy-, light-, and non-smokers were administered nicotine at 20, 40, and 60 minutes into an 80 minute session (Wesnes, et al 1983). This study compared the decline in sensitivity (vigilance) over time among the three groups, and found

that nicotine reduced the decline significantly. Furthermore, the authors demonstrated that the effect was independent of smoking status. That is, smokers who abstain before a performance task do not appear to be dependent on nicotine to regain their previous level of function. Smokers were not merely returning to their baseline performance since the heavy smokers, the light smokers, and the non-smokers responded similarly to nicotine administration.

Wesnes and Warburton (1983) cite an early study of selective attention by Tarriere and Hartemann (1964), which combined "central guiding with peripheral visual surveillance" over a 2 1/2 hour time period. They point out that, although smokers who were allowed to smoke during the experiment missed far fewer peripheral signals than did smokers who did not smoke, it was not clear whether this was at the expense of reduced vigilance on the central guiding task. Nonsmokers' performance was intermediate between that of the two smoking groups, although their selective attention decreased significantly over time.

The classic example of experiments on this perceptual intrusion is the Stroop test, which determines the time difference between naming colors in congruous and incongruous situations. Evidence from studies of the effect of nicotine on reducing distraction during performance of vigilance tasks is consistent with that from other

attention related studies (U.S.DHHS 1988). Knott (1985) investigated the role of tobacco as a "chemical stimulus filter" as reflected in electrocortical measures which are assumed to tap attentional processes. His study of female smokers revealed that tobacco-induced reductions of sensory evoked potentials differed by pre-experimental expired alveolar carbon monoxide (CO). The low CO group exhibited reduced potentials in the non-distracted experimental conditions, while the high CO group's reduction occurred only under the distracted condition.

The effects of nicotine on learning and memory, apart from its effect on attention, involve the acquisition, consolidation, and retention of information. Animal studies cited by Mangan (1983) suggest that nicotine facilitates learning and memory in all of these aspects, although the effect appears to be biphasic with smaller doses being facilitatory and larger ones inhibitory. Mangan (1983) found that there was an interaction between task difficulty and nicotine dosage resulting in impedance of learning an easy task and improvement at the same dose for learning a more difficult task. In contrast, he found that both low and medium doses enhanced recall in two types of learning tasks regardless of difficulty. Furthermore, data from Mangan and Golding (1983) suggest that the effect is to improve memory consolidation and is reflected in improvement of long-term, rather than short term memory.

In two experiments of memory encoding and nicotine. Warburton, et al (1986) found that learning, i.e. input of information to storage, was facilitated by nicotine, and that it produced state-dependent learning. That is, behavior learned in one pharmacologic state is better remembered when retention is tested in the same state. Lowe's (1986) experiment with a combination of alcohol and nicotine ingestion confirmed this finding. Warburton, et al (1986) suggest that the reason why some studies have failed to find nicotine-related memory improvement is that these studies utilized different pharmacologic states for learning and testing. Results from Peeke and Peeke (1984), who found no effect of nicotine on memory, exemplify this methodological problem. More recently, Ney, et al (1988) have shown that experimental conditions other than pharmacologic state may affect the results of studies of cognitive performance and their applicability to real life situations because smokers modulate their intake to contend with task conditions. Thus, results from studies with experimental designs in which smoking is regulated or is not monitored may not reflect the effects of nicotine outside of the laboratory.

Problem solving ability involves learning, memory, and rapid information processing in which performance is measured by the speed and accuracy of responses. Wesnes and Warburton (1983)

conducted two experiments to investigate the effects of of smoking on the performance of a rapid information processing task. The task involved detecting sequences of odd or even digits in a rapid series of psuedo-random digits. Their experiments on a small number of undergraduate volunteers demonstrated a greater improvement in performance after smoking a high nicotine cigarette than after lower nicotine cigarettes. In comparison with performance following a nicotine-free cigarette, nicotine-containing cigarettes improved performance. Furthermore, performance deteriorated over time among the subjects smoking nicotine-free cigarettes. Later experiments confirmed that higher yielding cigarettes produce greater improvements than lower yielding ones (Wesnes 1984b). These experiments were the first demonstration that smoking improves information processing performance above pre-smoking levels, rather than simply restoring it to those levels after abstinence. Other work by these authors (Wesnes 1984a , Wesnes & Revell 1984, Warburton 1984) supports the involvement of central cholinergic mechanisms in the processing of information in humans. Recent experimental evidence provides additional support to the involvement of the nicotinic cholinergic system in the processing of visual information or visual-motor function (London 1988).

Dunne, et al (1985) examined the effects of nicotine on problem solving performance among a group of non-smoking female

volunteers. The subjects were required to solve both numerical and verbal problems of varying difficulties. This experiment demonstrated impairment of both recall and recognition of information learned subsequent to chewing nicotine gum. Nicotine had no influence on overall problem solving performance. Thus, the effects of nicotine on information processing may be cue and context specific rather than facilitating general mental efficiency. Alternatively, the negative results may have been due to the relative inefficiency of chewing gum as a nicotine delivery system or to the use of non-smokers as experimental subjects.

For over sixty years, smoking has been known to affect motor control by increasing hand tremor and by decreasing reaction time (U.S. DHHS 1988). Nicotine is the pharmocologic agent in tobacco smoke which is responsible for this, as demonstrated by West and Jarvis (1986), who administered nasal nicotine solution to non-smokers and found strong and consistent enhancement of motor control. Myrsten and Anderson (1978) examined the effect of smoking on tasks involving simple and complex reaction time. Their findings were similar to results from studies of problem solving performance, in that smoking prevented the deterioration of performance over time for the simple reaction time periods (i.e. prevented an increase in reaction time) and significantly improved (i.e. reduced) reaction time for complex tasks compared to the non-smoking condition. Morgan

and Pickens (1982) investigated reaction time performance related to the smoking procedure used in various experiments. Although comparisons with non-smokers were not made, the authors found significantly slower reaction time associated with subjects' ad libitum smoking of their own cigarettes compared to ad libitum smoking or smoking with a prescribed puff pattern of standard cigarettes with higher nicotine content. While one might reasonably infer a nicotine dose-response relationship from this experiment, the importance of this work is in cautioning that experimental conditions may greatly affect the results of studies relating cigarette smoking to cognitive, behavioral, and physical function.

Well documented and perhaps one of the most important positive effects of nicotine is its apparent usefulness in an individual's ability to control response to stressors (Gilbert 1979). This is accomplished through reduction of negative feelings or emotions (or in psychological terms, negative affect) and enhancement of positive ones. However, Lombardo and Epstein (1986) have pointed out that because nicotine also increases sympathetic nervous system activity, empirical research on the physiology of emotion suggests that nicotine should increase negative affect. They tested one hypothesized explanation for this paradox, i.e. interference by nicotine with the perception of autonomic arousal, and failed to find support. It is likely that a smoker's perception or expectation of the

relaxing effect of cigarette smoking determines its actual effect to a some degree. If this is the result of a conditioned response, then a study's failure to find such an effect (Hatch 1983) may be due to the parameters of an experimental setting.

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